

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

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SANOFI-AVENTIS U.S. LLC,  
AVENTIS PHARMA S.A. and  
SANOFI

Plaintiffs,

v.

ONCO THERAPIES LIMITED

Defendant.

C.A. No.: \_\_\_\_\_

*Electronically Filed*

**COMPLAINT FOR PATENT INFRINGEMENT**

Plaintiffs Sanofi-Aventis U.S. LLC (hereinafter “Sanofi U.S.”), Aventis Pharma S.A. (hereinafter “Aventis”) and Sanofi (collectively, “Plaintiffs”) for their Complaint against defendant Onco Therapies Limited (hereinafter “Onco” or “Defendant”), hereby allege as follows:

## **THE PARTIES**

1. Plaintiff Sanofi U.S. is a U.S. subsidiary of Sanofi and is a company organized and existing under the laws of the State of Delaware, having commercial headquarters at 55 Corporate Drive, Bridgewater, New Jersey 08807.

2. Plaintiff Aventis is a corporation organized and existing under the laws of France, having its principal place of business at 20 avenue Raymond Aron, 92160 Antony, France.

3. Plaintiff Sanofi is a corporation organized and existing under the laws of France, having its principal place of business at 54 rue La Boétie, 75008 Paris, France.

4. Plaintiff Sanofi is a global research-driven pharmaceutical company that discovers, develops, manufactures and markets a broad range of innovative products to improve human and animal health.

5. On information and belief, Onco is a corporation organized and existing under the laws of India, having its principal place of business at Strides House, Bilekahalli, Bannerghatta Road, Bangalore, Karnataka 560076, India.

6. On information and belief, Onco is a wholly-owned subsidiary of Strides Arcolab Limited (hereinafter “Arcolab”). On information and belief, Arcolab is a corporation organized and existing under the laws of India, having its principal place of business at Strides House, Bilekahalli, Bannerghatta Road, Bangalore, Karnataka 560076, India.

7. On information and belief, Onco conducts business through and with Agila Specialties Inc. (hereinafter “Agila”), formerly known as Strides, Inc. On information and belief, Agila is a corporation organized and existing under the laws of New Jersey, having its principal place of business at 201 South Main Street, Suite 3, Lambertville, New Jersey 08530. On information and belief, Agila is an agent or affiliate of Onco.

8. On information and belief, Onco conducts business through and with Strides Pharma Inc. (hereinafter “Strides Pharma”). On information and belief, Strides Pharma is a corporation organized and existing under the laws of New Jersey, having its principal place of business at 201 South Main Street, Suite 3, Lambertville, New Jersey 08530. On information and belief, Strides Pharma is a wholly-owned subsidiary of Arcolab. On information and belief, Strides Pharma is an agent or affiliate of Onco.

9. On information and belief, Onco assembled and caused to be filed with the United States Food and Drug Administration (“FDA”), pursuant to 21 U.S.C. § 355(j) (Section 505(j) of the Federal Food, Drug and Cosmetic Act), Abbreviated New Drug Application (“ANDA”) No. 207381 (hereinafter “the Onco ANDA”) concerning a proposed drug product, cabazitaxel injection [60 mg/1.5 mL] [40 mg/mL] (“Onco’s Proposed ANDA Product”).

#### **JURISDICTION AND VENUE**

10. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

11. This Court has personal jurisdiction over Onco. On information and belief, Onco conducts business through and with Agila. On information and belief, Agila is a corporation organized and existing under the laws of New Jersey, having its principal place of business at 201 South Main Street, Suite 3, Lambertville, New Jersey 08530. On information and belief, Agila is registered with the New Jersey Department of Treasury under entity identification number 0100791546. On information and belief, Agila maintains a registered corporate agent at 37 Veronica Avenue, Somerset, New Jersey 08873. On information and belief, Agila is an agent or affiliate of Onco. On information and belief, Onco conducts business

through and with Strides Pharma. On information and belief, Strides Pharma is a corporation organized and existing under the laws of New Jersey, having its principal place of business at 201 South Main Street, Suite 3, Lambertville, New Jersey 08530. On information and belief, Strides Pharma is registered with the New Jersey Department of Treasury under entity identification number 0400580219. On information and belief, Strides Pharma maintains a registered corporate agent at 201 South Main Street, Suite 3, Lambertville, New Jersey 08530. On information and belief, Strides Pharma holds an active wholesale drug and medical device license for the State of New Jersey under License No. 5004572.

12. On information and belief, Onco directly or through its affiliates and agents develops, formulates, manufactures, markets, imports and sells pharmaceutical products, including generic drug products, which are copies of products invented and developed by innovator pharmaceutical companies, throughout the United States, including in this Judicial District.

13. On information and belief, Onco has affiliations with the State of New Jersey that are pervasive, continuous, and systematic. On information and belief, Onco engages in direct marketing, distribution, and/or sale of generic pharmaceutical drugs within the State of New Jersey and to the residents of the State of New Jersey.

14. On information and belief, Onco regularly conducts and/or solicits business, directly, or through its parent company, Arcolab, and/or affiliate or subsidiary companies, Agila, and Strides Pharma, in the State of New Jersey. On information and belief, Onco engages in other persistent courses of conduct, directly, or through its parent company, Arcolab, and/or affiliate or subsidiary companies, Agila, and Strides Pharma, in the State of New

Jersey, and/or derives substantial revenue from services or things used or consumed in the State of New Jersey.

15. Onco is also subject to personal jurisdiction in the State of New Jersey because, *inter alia*, Onco has committed, aided, abetted, contributed to, and/or participated in the commission of a tortious act of patent infringement under 35 U.S.C. § 271(e)(2) that has led and/or will lead to foreseeable harm and injury to Plaintiff Sanofi U.S., having commercial headquarters in the State of New Jersey. In its December 4, 2014 Paragraph IV Notice Letter, Onco states that it intends to engage in the commercial manufacture, use, and/or sale of Onco's Proposed ANDA Product before the expiration of U.S Patent Nos. 5,847,170 ("170 patent") and 7,241,907 ("907 patent") throughout the United States, including in this Judicial District.

16. In the alternative, Onco is subject to jurisdiction in the United States under the principles of general jurisdiction, and specially in the State of New Jersey pursuant to Fed. R. Civ. P. 4(k)(2). Onco has contacts with the United States by, *inter alia*, its having filed an ANDA with the FDA.

17. On information and belief, upon approval of the Onco ANDA, Onco and/or its affiliates, agents or subisdiaries will market, sell and/or distribute Onco's Proposed ANDA Product throughout the United States, including in this Judicial District, and will derive substantial revenue therefrom.

18. On information and belief, upon approval of the Onco ANDA, Onco and/or its affiliates, agents or subsidiaries will place Onco's Proposed ANDA Product into the stream of commerce with the reasonable expectation or knowledge and the intent that such product will ultimately be purchased and used by consumers in this Judicial District.

19. Venue is proper in this Court at least pursuant to 28 U.S.C. §§ 1391(b), (c), and/or (d), and 1400(b).

**THE PATENTS-IN-SUIT**

20. Sanofi U.S. holds approved New Drug Application (“NDA”) No. 201023 for cabazitaxel injection, 60 mg/ 1.5 mL (40 mg/mL), which is prescribed and sold in the United States under the trademark JEVTANA® KIT (hereinafter “JEVTANA®”). The U.S. Food and Drug Administration (“FDA”) approved NDA No. 201023 on June 17, 2010. JEVTANA® is approved for use in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

21. United States Patent No. 5,847,170 (the “’170 patent,” copy attached as Exhibit A) is entitled “Taxoids, Their Preparation And Pharmaceutical Compositions Containing Them” and was duly and legally issued by the United States Patent and Trademark Office (“USPTO”) on December 8, 1998. The ’170 patent claims, *inter alia*, cabazitaxel and pharmaceutical compositions containing cabazitaxel. The ’170 patent is listed in the FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the “Orange Book”) for JEVTANA® (NDA No. 201023).

22. The ’170 patent is owned by Aventis.

23. United States Patent No. 7,241,907 (the “’907 patent,” copy attached as Exhibit B) is entitled “Acetone Solvate of Dimethoxy Docetaxel and its Process of Preparation” and was duly and legally issued by the United States Patent and Trademark Office (“USPTO”) on July 10, 2007. The ’907 patent claims, *inter alia*, an acetone solvate of cabazitaxel. The ’907 patent is listed in the FDA’s Orange Book for JEVTANA® (NDA No. 201023).

24. The '907 patent is owned by Aventis.

**CLAIMS FOR RELIEF – PATENT INFRINGEMENT**

25. On information and belief, Onco submitted the Onco ANDA to the FDA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Onco's Proposed ANDA Product.

26. On information and belief, the Onco ANDA seeks FDA approval of Onco's Proposed ANDA Product for use in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

27. On information and belief, Onco actively participated in and/or directed activities related to the submission of the Onco ANDA and the development of Onco's Proposed ANDA Product, was actively involved in preparing the ANDA, and/or intends to directly benefit from and has a financial stake in the approval of the ANDA. On information and belief, upon approval of the Onco ANDA, Onco will be involved in the manufacture, distribution, and/or marketing of Onco's Proposed ANDA Product.

28. By letter dated December 4, 2014 (the "December 4 Letter"), and pursuant to 21 U.S.C. § 355(j)(2)(B)(ii) and 21 C.F.R. §314.95, Onco notified Plaintiffs that it had submitted to the FDA the Onco ANDA, seeking approval to engage in the commercial manufacture, use, or sale of Onco's Proposed ANDA Product before the expiration of the '170 patent and the '907 patent. The December 4 Letter was received by Plaintiffs on December 5, 2014.

29. In its December 4 Letter, Onco notified Plaintiffs, as part of the Onco ANDA, it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a

“Paragraph IV Certification”) with respect to the ’170 patent and the ’907 patent. On information and belief, Onco certified that, the ’170 patent and the ’907 patent are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Onco’s Proposed ANDA Product.

30. The Onco ANDA refers to and relies upon the Sanofi U.S.’s NDA No. 201023 for JEVVTANA®.

31. In the December 4 Letter, Onco offered confidential access to portions of the Onco ANDA on terms and conditions set forth in paragraph 2 of the December 4 Letter (“Onco Offer”). Onco requested that Plaintiffs accept the Onco Offer before receiving access to any portion of the Onco ANDA. The Onco Offer contained unreasonable restrictions that would apply under a protective order. For example, the Onco Offer required that Plaintiffs’ outside counsel do not engage, formally or informally, in any patent prosecution or any FDA counseling, litigation or other work before or involving the FDA on behalf of Plaintiffs.

32. Under 21 U.S.C. § 355(j)(5)(C)(i)(III), an “offer of confidential access shall contain such restrictions . . . on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information.”

33. Since rejecting the Onco Offer, Plaintiffs attempted to negotiate with Onco to obtain a copy of excerpts of the Onco ANDA under restrictions “as would apply had a protective order been issued.” Those negotiations were unsuccessful. For example, Onco’s final proposal continued to unreasonably impose patent prosecution and FDA restrictions on Plaintiffs’ outside counsel.

34. Plaintiffs are not aware of any other means of obtaining information regarding Onco's Proposed ANDA Product within the 45-day statutory period. Without such information, Plaintiffs will use the judicial process and the aid of discovery to obtain, under appropriate judicial safeguards such information as is required to confirm its allegations of infringement and to present to the Court evidence that Onco's Proposed ANDA Product falls within the scope of one or more claims of the '170 and '907 patents.

**COUNT I**

**INFRINGEMENT OF U.S. PATENT NO. 5,847,170**

35. Plaintiff repeats and realleges paragraphs 1 through 34 above as if fully set forth herein.

36. By submitting the Onco ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Onco's Proposed ANDA Product throughout the United States prior to the expiration of the '170 patent, Onco committed an act of infringement of the '170 patent under 35 U.S.C. § 271(e)(2). On information and belief, Onco was aware of the '170 patent at the time the Onco ANDA was submitted.

37. If Onco commercially makes, uses, offers to sell, or sells Onco's Proposed ANDA Product within the United States, or imports Onco's Proposed ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '170 patent, it would further infringe the '170 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

38. Plaintiffs will be irreparably harmed if Onco is not enjoined from infringing the '170 patent. Plaintiffs do not have an adequate remedy at law.

39. Onco's certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '170 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

**COUNT II**

**INFRINGEMENT OF U.S. PATENT NO. 7,241,907**

40. Plaintiffs repeat and reallege paragraphs 1 through 39 above as if fully set forth herein.

41. By submitting the Onco ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Onco's Proposed ANDA Product throughout the United States prior to the expiration of the '907 patent, Onco committed an act of infringement of the '907 patent under 35 U.S.C. § 271(e)(2). On information and belief, Onco was aware of the '907 patent at the time the Onco ANDA was submitted.

42. If Onco commercially makes, uses, offers to sell, or sells Onco's Proposed ANDA Product within the United States, or imports Onco's Proposed ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '907 patent, it would further infringe the '907 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

43. Plaintiffs will be irreparably harmed if Onco is not enjoined from infringing the '907 patent. Plaintiffs do not have an adequate remedy at law.

44. Onco's certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '907 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

**PRAAYER FOR RELIEF**

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Onco Therapies Limited has infringed one or more claims of the '170 patent by filing ANDA No. 207381 relating to Onco's Proposed ANDA Product before the expiration of the '170 patent;

B. A judgment that the manufacture, use, offer for sale, sale and/or importation of Onco's Proposed ANDA Product will infringe the '170 patent;

C. A judgment declaring that the '170 patent remains valid and enforceable;

D. A permanent injunction restraining and enjoining Onco Therapies Limited, and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Onco's Proposed ANDA Product until the expiration of the '170 patent or any later date of exclusivity to which Plaintiffs and/or the '170 patent are or become entitled to;

E. An order that the effective date of any approval of Onco's ANDA No. 207381 relating to Onco's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '170 patent or any later date of exclusivity to which Plaintiffs and/or the '170 patent are or become entitled;

F. A judgment that Onco Therapies Limited has infringed one or more claims of the '907 patent by filing ANDA No. 207381 relating to Onco's Proposed ANDA Product before the expiration of the '907 patent;

G. A judgment that the manufacture, use, offer for sale, sale and/or importation of Onco's Proposed ANDA Product will infringe the '907 patent;

H. A judgment declaring that the '907 patent remains valid and enforceable;

I. A permanent injunction restraining and enjoining Onco Therapies Limited, and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Onco's Proposed ANDA Product until the expiration of the '907 patent or any later date of exclusivity to which Plaintiffs and/or the '907 patent are or become entitled to;

J. An order that the effective date of any approval of Onco's ANDA No. 207381 relating to Onco's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '907 patent or any later date of exclusivity to which Plaintiffs and/or the '907 patent are or become entitled;

K. A declaration that this case is "exceptional" within the meaning of 35 U.S.C. § 285 and an award of reasonable attorney fees, costs, expenses, and disbursements of this action; and

L. Such other and further relief as the Court may deem just and proper.

January 14, 2015

Respectfully submitted,

By: s/Liza M. Walsh

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**RULE 11.2 CERTIFICATION**

I, Liza M. Walsh, admitted to the bars of the State of New Jersey and this Court, and a Partner in the law firm of Connell Foley LLP representing Plaintiffs Sanofi-Aventis U.S. LLC, Aventis Pharma S.A. and Sanofi in the above-captioned matter, hereby certify pursuant to L. Civ. R. 11.2 that the matter in controversy in this action is related to the following actions that are pending before the District Court for the District of New Jersey: *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-7869 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Accord Healthcare, Inc.*, C. A. No. 14-8079 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. BPI Labs, LLC et al.*, C. A. No. 14-8081 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-8082 (MAS)(LHG); the following actions pending before the District Court for the District of Delaware: *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-1496 (LPS); and *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-1533 (LPS); one pending litigation in the District Court for the Middle District of Florida: *Sanofi-Aventis U.S. LLC et al. v. BPI Labs, LLC et al.*, C. A. No. 14-3233 (EAK)(TGW); and one pending litigation in the District Court for the Middle District of North Carolina: *Sanofi-Aventis U.S. LLC et al. v. Accord Healthcare, Inc.*, C. A. No. 15-0018 (NCT)(LPA).

I certify under penalty of perjury that the foregoing is true and correct.

January 14, 2015

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**RULE 201.1 CERTIFICATION**

We hereby certify that the above-captioned matter is not subject to compulsory arbitration in that the plaintiffs seek, inter alia, injunctive relief.

January 14, 2015

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# **EXHIBIT A**



US005847170A

# United States Patent [19]

Bouchard et al.

[11] Patent Number: 5,847,170  
 [45] Date of Patent: Dec. 8, 1998

[54] TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[75] Inventors: Hervé Bouchard, Ivry-sur-Seine; Jean-Dominique Bourzat, Vincennes; Alain Commerçon, Vitry-sur-Seine, all of France

[73] Assignee: Rhône-Poulenc Rorer, S.A., Antony Cedex, France

[21] Appl. No.: 622,011

[22] Filed: Mar. 26, 1996

### Related U.S. Application Data

[60] Provisional application No. 60/010,144, Jan. 17, 1996.

### Foreign Application Priority Data

Mar. 27, 1995 [FR] France ..... 95 03545  
 Dec. 22, 1995 [FR] France ..... 95 15381

[51] Int. Cl.<sup>6</sup> ..... C07D 305/14

[52] U.S. Cl. ..... 549/510; 549/511

[58] Field of Search ..... 549/510, 511

### References Cited

#### U.S. PATENT DOCUMENTS

5,229,526	7/1993	Holton et al. ....	549/213
5,319,112	6/1994	Kingston et al. ....	549/510
5,486,601	1/1996	Holton et al. ....	514/337
5,739,362	4/1998	Holton et al. ....	549/510

#### FOREIGN PATENT DOCUMENTS

0 336 841	10/1989	European Pat. Off. .
604910	7/1994	European Pat. Off. .
0 639 577	2/1995	European Pat. Off. .
694539	1/1996	European Pat. Off. .
WO 92/09589	6/1992	WIPO .
WO 94/07878	4/1994	WIPO .
WO 94/18164	8/1994	WIPO .
WO96/00724	1/1996	WIPO .

### OTHER PUBLICATIONS

Greene et al., "Protective Groups in Organic Synthesis", pp. 10–14, 2<sup>nd</sup> edition, 1991.

M.L. Shelanski et al., "Microtubule Assembly in the Absence of Added Nucleotides", Proc. Natl. Acad. Sci. vol. 70, No. 3, pp. 765–768 (1973).

G. Chauvière et al., "Analyse structurable et étude biochimique de produits isolés de l'if: Taxus baccata L. (Taxaceæ)", C.R. Acad. Sc. Paris, t.293, pp. 501–503 (1981).

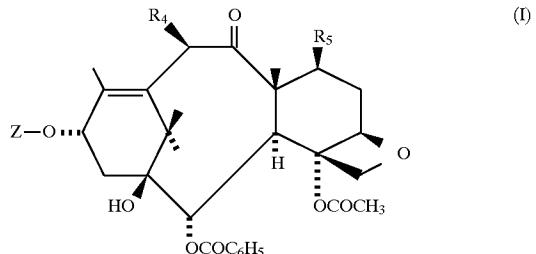
J. Kant et al., "A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaicatin III. Synthesis and Biological Properties of Novel C-10 Taxol Analogues", Tetrahedron Letters, vol. 35, No. 31, pp. 5543–5546, 1994.

Primary Examiner—Ba K. Trinh

Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.P.

### ABSTRACT

New taxoids of general formula (I):



their preparation and pharmaceutical compositions containing them, and the new products of general formula (I) in which Z represents a radical of general formula (II):



display noteworthy antitumour and antileukaemic properties.

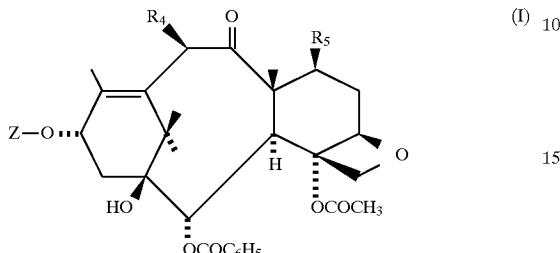
**22 Claims, No Drawings**

1

**TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

This application claims the priority of U.S. provisional application 60/010,144 filed Jan. 17, 1996.

The present invention relates to new taxoids of general formula (I)



in which:

Z represents a hydrogen atom or a radical of general formula (II):



in which:

R<sub>1</sub> represents

a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms and trifluoromethyl radicals,

a thenoyl or furoyl radical or

a radical R<sub>2</sub>—O—CO— in which R<sub>2</sub> represents:

an alkyl radical containing 1 to 8 carbon atoms,

an alkenyl radical containing 2 to 8 carbon atoms,

an alkynyl radical containing 3 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a cycloalkenyl radical containing 4 to 6 carbon atoms or

a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or

more substituents selected from halogen atoms, hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino radicals, morpholino radicals, 1-piperazinyl radicals, said piperazinyl radicals being optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, cycloalkyl radicals containing 3 to 6

carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals, said phenyl radicals being optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms, cyano radicals, carboxyl radicals and alkoxy carbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4

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carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical preferably selected from furyl and thiényl radicals, or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, R<sub>3</sub> represents

an unbranched or branched alkyl radical containing 1 to 8 carbon atoms,

an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms,

an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxy carbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxy carbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, dialkylamino, alkoxy carbonylamino, acyl, aryl carbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxy carbonyl radicals,

with the understanding that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R<sub>4</sub> represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with one or

more substituents selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkoxy carbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms, or both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, said saturated 5- or 6-membered heterocyclic radical optionally being substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

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$R_5$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyoxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

Preferably, the aryl radicals which can be represented by  $R_3$  are phenyl or  $\alpha$ - or  $\beta$ -naphthyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms (fluorine, chlorine, bromine, iodine) alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or  $\alpha$ - or  $\beta$ -naphthyl radicals.

Preferably, the heterocyclic radicals which can be represented by  $R_3$  are 5-membered aromatic heterocyclic radicals containing one or more identical or different atoms selected from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents selected from halogen atoms (fluorine, chlorine, bromine, iodine), alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 or 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 or 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 or 10 carbon atoms, cyano radicals, carboxyl radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms, and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

Preferably, the radicals  $R_4$  and  $R_5$ , which may be identical or different, represent unbranched or branched alkoxy radicals containing 1 to 6 carbon atoms, optionally substituted with a methoxy, ethoxy, ethylthio, carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-

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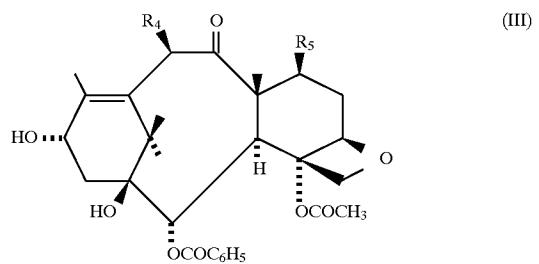
dimethylcarbamoyl, N,N-diethylcarbamoyl, N-pyrrolidinocarbonyl or N-piperidinocarbonyl radical.

More particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which  $R_1$  represents a benzoyl radical or a radical  $R_2-O-CO-$  in which  $R_2$  represents a tert-butyl radical and  $R_3$  represents an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from from halogen atoms (fluorine, chlorine), alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxycarbonylamino (tert-butoxycarbonylamino), trifluoromethyl, a 2-furyl radical, a 3-furyl radical, a 2-thienyl radical, a 3-thienyl radical, a 2-thiazolyl radical, a 4-thiazolyl radical, and a 5-thiazolyl radical, and  $R_4$  and  $R_5$ , which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

Still more particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which  $R_1$  represents a benzoyl radical or a radical  $R_2-O-CO-$  in which  $R_2$  represents a tert-butyl radical and  $R_3$  represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, and  $R_4$  and  $R_5$ , which may be identical or different, each represent a methoxy, ethoxy or propoxy radical.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumour and antileukaemic properties.

According to the present invention, the new products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by esterification of a product of general formula (III):



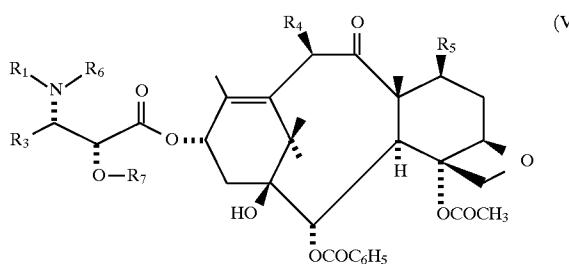
in which  $R_4$  and  $R_5$  are defined as above, by means of an acid of general formula (IV):



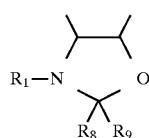
in which  $R_1$  and  $R_3$  are defined as above, and either  $R_6$  represents a hydrogen atom and  $R_7$  represents a group protecting the hydroxyl function, or  $R_6$  and  $R_7$  together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, to obtain an ester of general formula (V):

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in which  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  and  $R_7$  are defined as above, followed by replacement of the protective groups represented by  $R_7$  and/or  $R_6$  and  $R_7$  by hydrogen atoms.

The esterification by means of an acid of general formula (IV) may be performed in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridines) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature from  $-10^\circ$  to  $90^\circ$  C.

The esterification may also be carried out using the acid of general formula (IV) in the form of the symmetrical anhydride, working in the presence of an activating agent (aminopyridines) in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from  $0^\circ$  to  $90^\circ$  C.

The esterification may also be carried out using the acid of general formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base (tertiary aliphatic amine), working in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from  $0^\circ$  to  $80^\circ$  C.

Preferably,  $R_6$  represents a hydrogen atom and  $R_7$  represents a group protecting the hydroxyl function, or alternatively  $R_6$  and  $R_7$  together form a saturated 5- or 6-membered heterocycle.

When  $R_6$  represents a hydrogen atom,  $R_7$  preferably represents a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, trimethylsilyl, triethylsilyl,  $\beta$ -trimethylsilylethoxymethyl, benzyloxycarbonyl or tetrahydropyranyl radical.

When  $R_6$  and  $R_7$  together form a heterocycle, the latter is preferably an oxazolidine ring optionally monosubstituted or gem-disubstituted at position 2.

Replacement of the protective groups  $R_7$  and/or  $R_6$  and  $R_7$  by hydrogen atoms may be performed, depending on their nature, in the following manner:

- 1) when  $R_8$  represents a hydrogen atom and  $R_7$  represents a group protecting the hydroxyl function, replacement of the protective groups by hydrogen atoms is performed by means of an inorganic acid (hydrochloric acid, sulphuric acid, hydrofluoric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons or nitriles at a temperature of from  $-10^\circ$  to  $60^\circ$  C., or by means of a source of fluoride ions such as a hydrofluorine acid/triethylamine complex, or by catalytic hydrogenation,

- 2) when  $R_6$  and  $R_7$  together form a saturated 5- or 6-membered heterocycle, and more especially an oxazolidine ring of general formula (VI):

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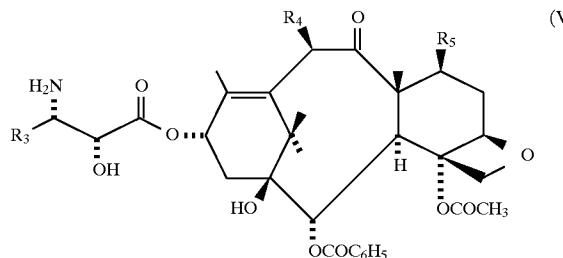
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in which  $R_1$  is defined as above and  $R_6$  and  $R_9$ , which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively  $R_8$  represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted with a trihalomethyl radical such as trichloromethyl and  $R_9$  represents a hydrogen atom, or alternatively  $R_8$  and  $R_9$ , together with the carbon atom to which they are linked, form a 4- to 7-membered ring, replacement of the protective group formed by  $R_6$  and  $R_7$  by hydrogen atoms may be performed, depending on the meanings of  $R_1$ ,  $R_8$  and  $R_9$ , in the following manner:

- a) when  $R_1$  represents a tert-butoxycarbonyl radical and  $R_8$  and  $R_9$ , which may be identical or different, represent an alkyl radical or an aralkyl (benzyl) or aryl (phenyl) radical, or alternatively  $R_8$  represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and  $R_9$  represents a hydrogen atom, or alternatively  $R_8$  and  $R_9$  together form a 4- to 7-membered ring, treatment of the ester of general formula (V) with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, yields the product of general formula (VII):



in which  $R_3$ ,  $R_4$  and  $R_5$  are defined as above, which is acylated by means of benzoyl chloride in which the phenyl ring is optionally substituted or by means of thenoyl chloride, or furoyl chloride or of a product of general formula:



in which  $R_2$  is defined as above and X represents a halogen atom (fluorine, chlorine) or a residue —O—R<sub>2</sub> or —O—CO—O—R<sub>2</sub>, to obtain a product of general formula (I) in which Z represents a radical of general formula (II).

Preferably, the product of general formula (V) is treated with formic acid at a temperature in the region of  $20^\circ$  C. to yield the product of general formula (VII).

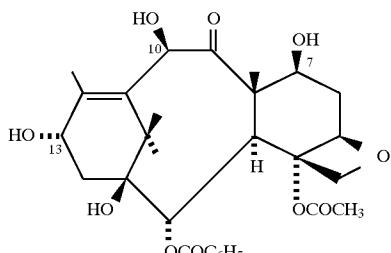
Preferably, the acylation of the product of general formula (VII) by means of a benzoyl chloride in which the phenyl radical is optionally substituted or by means of thenoyl chloride, or furoyl chloride or of a product of general formula (VIII) is performed in an inert organic solvent

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chosen from esters such as ethyl acetate, isopropyl acetate or n-butyl acetate and halogenated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane, in the presence of an inorganic base such as sodium bicarbonate or an organic base such as triethylamine. The reaction is performed at a temperature of from 0° to 50° C., and preferably at about 20° C.

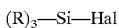
b) when R<sub>1</sub> represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R<sub>2</sub>O—CO— in which R<sub>2</sub> is defined as above, R<sub>8</sub> represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R<sub>9</sub> represents a hydrogen atom, replacement of the protective group formed by R<sub>6</sub> and R<sub>7</sub> by hydrogen atoms is performed in the presence of an inorganic acid (hydrochloric acid, sulphuric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed in a stoichiometric or catalytic amount, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from -10° to 60° C., and preferably from 15° to 30° C.

According to the invention, the products of general formula (III), that is to say the products of general formula (I) in which Z represents a hydrogen atom and R<sub>4</sub> and R<sub>5</sub> are defined as above, may be obtained from 10-deacetylbaccatin III of formula (IX):



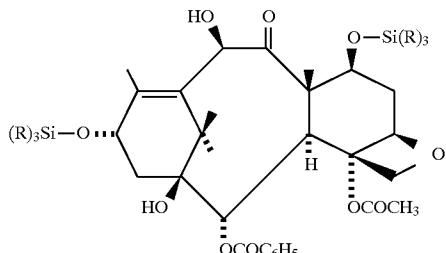
(IX)

It can be especially advantageous to protect the hydroxyl functions at the positions 7 and 13 selectively, for example in the form of a silyl diether which may be obtained by the action of a silyl halide of general formula:



(X)

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, on 10-deacetylbaccatin III, to obtain a product of general formula (XI):



(XI)

in which R is defined as above, followed by the action of a product of general formula:



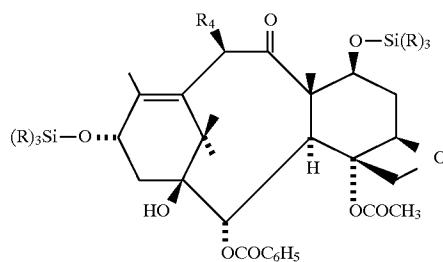
(XII)

in which R'<sub>4</sub> represents a radical such that R'<sub>4</sub>—O is identical to R<sub>4</sub> defined as above and X<sub>1</sub> represents a reactive

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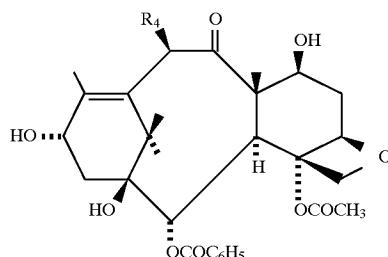
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ester residue such as a sulphuric or sulphonate ester residue or a halogen atom, to obtain a product of general formula (XIII):



(XIII)

in which R and R<sub>4</sub> are defined as above, the silyl protective groups of which are replaced by hydrogen atoms to obtain a product of general formula (XIV):



(XIV)

in which R<sub>4</sub> is defined as above, which is etherified selectively at position 7 by the action of a product of general formula:



(XV)

in which R'<sub>5</sub> represents a radical such that R'<sub>5</sub>—O is identical to R<sub>5</sub> defined as above and X<sub>2</sub> represents a halogen atom or a reactive ester residue such as a sulphuric or sulphonate ester residue, to give the product of general formula (III).

Generally, the action of a silyl derivative of general formula (X) on 10-deacetylbaccatin III is performed in pyridine or triethylamine, where appropriate in the presence of an organic solvent such as an aromatic hydrocarbon, for instance benzene, toluene or xylenes, at a temperature between 0° C. and the refluxing temperature of the reaction mixture.

Generally, the action of a product of general formula (XII) on a product of general formula (XI) is performed, after metalation of the hydroxyl function at position 10 by means of an alkali metal hydride, such as sodium hydride, an alkali metal amide, such as lithium amide, or an alkali metal alkylide, such as butyllithium, working in an organic solvent, such as dimethylformamide or tetrahydrofuran, at a temperature of from 0° to 50° C.

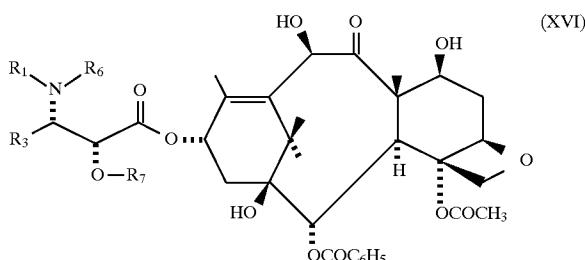
Generally, the replacement of the silyl protective groups of the product of general formula (XIII) by hydrogen atoms is performed by means of an acid such as hydrofluoric acid or trifluoroacetic acid in the presence of a base such as triethylamine or pyridine optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, the base optionally being combined with an inert organic solvent such as a nitrile, for instance acetonitrile, or a halogenated aliphatic hydrocarbon, such as dichloromethane, at a temperature of from 0° to 80° C.

Generally, the action of a product of general formula (XV) on a product of general formula (XIV) is performed under the conditions described above for the action of a product of general formula (XII) on a product of general formula (XI).

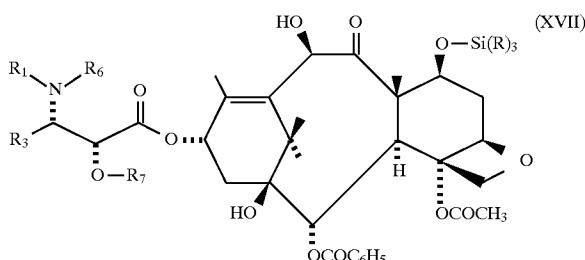
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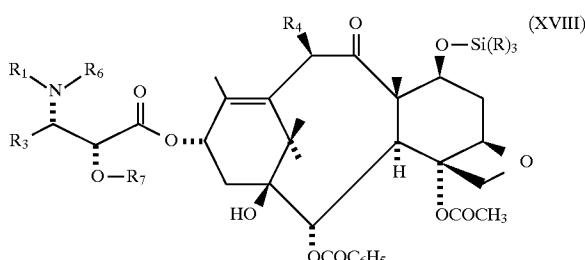
According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), R<sub>4</sub> is defined as above and R<sub>5</sub> is defined as above may be obtained from a product of general formula (XVI):



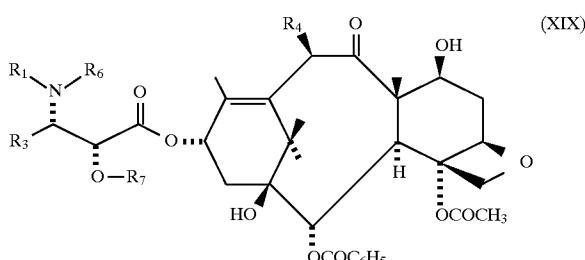
in which R<sub>1</sub>, R<sub>3</sub>, R<sub>6</sub> and R<sub>7</sub> are defined as above, by silylation at position 7 by means of a product of general formula (X), to obtain a product of general formula (XVII):



in which R, R<sub>1</sub>, R<sub>3</sub>, R<sub>6</sub> and R<sub>7</sub> are defined as above, which is functionalized at position 10 by means of a product of general formula (XII) to give a product of general formula (XVIII):



in which R, R<sub>1</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub> and R<sub>7</sub> are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula (XIX):

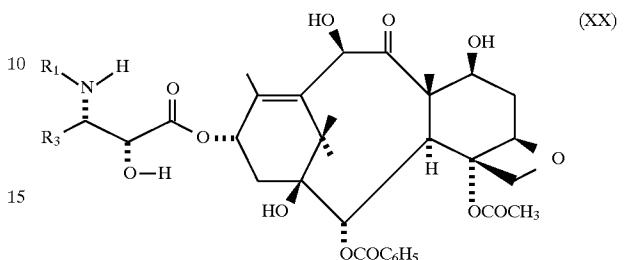


which, by the action of a product of general formula (XV), yields the product of general formula (V), the protective groups of which are replaced by hydrogen atoms to give a product of general formula (I) in which Z represents a radical of general formula (II).

The reactions used for silylation, functionalization and replacement of the protective groups by hydrogen atoms are performed under conditions similar to those described above.

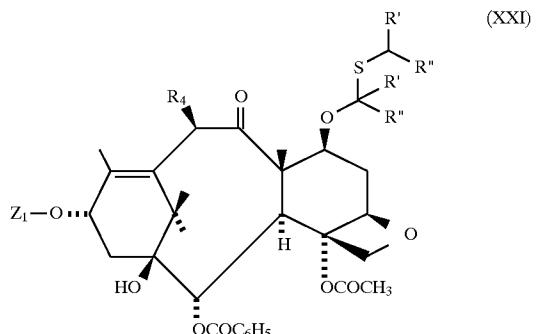
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The products of general formula (XVI) may be obtained under the conditions described in European Patent EP 0,336, 841 and international Applications PCT WO 92/09589 and WO 94/07878, the disclosures of which are hereby incorporated by reference in their entirety, or from the products of general formula (XX):



in which R<sub>1</sub> and R<sub>3</sub> are defined as above, according to known methods for protecting the hydroxyl function of the side chain without affecting the remainder of the molecule.

According to the invention, the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether such as tetrahydrofuran or dioxane, on a product of general formula (XXI):



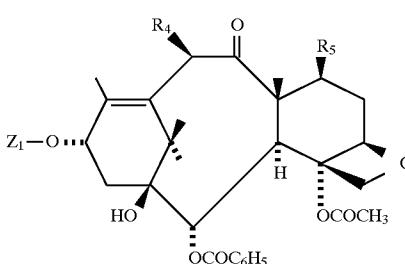
in which R<sub>4</sub> is defined as above and R' and R'', which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R'', together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z<sub>1</sub> represents a hydrogen atom or a radical of general formula (XXII):



in which R<sub>1</sub>, R<sub>3</sub>, R<sub>6</sub> and R<sub>7</sub> are defined as above, and, to obtain a product of general formula (XXIII):

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(XXIII)

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cell line selected for its resistance to doxorubicin (DOX) which expresses mdr 1.

The examples which follow illustrate the present invention.

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## EXAMPLE 1

126 mg of dicyclohexylcarbodiimide and then 14 mg of 4-(N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 217.8 mg of 4α-acetoxy-2α-benzyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene, 200 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 2 cm<sup>3</sup> of ethyl acetate. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 16 hours, and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. The residue obtained was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2 cm in diameter (elution gradient: ethyl acetate:dichloromethane from 10:90 to 40:60 by volume), collecting 10-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 271.8 mg of 4α-acetoxy-2α-benzyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white solid, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub> with a few drops of CD<sub>3</sub>OD-d<sub>4</sub>; chemical shifts δ in ppm; coupling constants J in Hz): 1.02 (s, 9H: C(CH<sub>3</sub>)<sub>3</sub>); 1.10 (s, 3H: CH<sub>3</sub>); 1.17 (s, 3H: CH<sub>3</sub>); 1.63 (s, 3H: CH<sub>3</sub>); from 1.65 to 1.85 and 2.60 (2 mts, 1H each; CH<sub>2</sub> at position 6); 1.78 (unres. comp., 3H: CH<sub>3</sub>); 2.02 and 2.15 (2 dd, J=14 and 9, 1H each: CH<sub>2</sub> at position 14); 2.14 (s, 3H: CH<sub>3</sub>); 3.22 and 3.35 (2 s, 3H each: OCH<sub>3</sub>); 3.64 (d, J=7, 1H: H at position 3); 3.73 (mt, 1H: H at position 7); 3.76 (s, 3H: ArOCH<sub>3</sub>); 4.06 and 4.16 (2 d, J=8.5, 1H each; CH<sub>2</sub> at position 20); 4.53 (d, J=5, 1H: H at position 2); 4.67 (s, 1H: H at position 10); 4.85 (broad d, J=10, 1H: H at position 5); 5.36 (mt, 1H: H at position 3'); 5.52 (d, J=7, 1H: H at position 2); 6.07 (mt, 1H: H at position 13); 6.33 (unres. comp., 1H: H at position 5'); 6.88 (d, J=8, 2H: aromatic H at the ortho position with respect to OCH<sub>3</sub>); from 7.25 to 7.40 (mt, 7H: aromatic H at position 3' and aromatic H at the meta position with respect to OCH<sub>3</sub>); 7.43 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.58 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 7.96 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

A solution of 446.3 mg of 4α-acetoxy-2α-benzyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 11.6 cm<sup>3</sup> of a 0.1N solution of hydrogen chloride in ethanol was stirred constantly at a temperature in the region of 0° C. for 16 hours under an argon atmosphere. The reaction mixture was then diluted with 40 cm<sup>3</sup> of dichloromethane and 5 cm<sup>3</sup> of distilled water. After settling had taken place, the aqueous phase was separated and extracted with 5 cm<sup>3</sup> of dichloromethane. The organic phases were combined, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 424.2 mg of a pale yellow solid were obtained, which product was purified by preparative thin-layer chromatog-

followed, when Z<sub>1</sub> represents a radical of general formula (XXII), that is to say when the product of general formula (XXIII) is identical to the product of general formula (V), by replacement of the protective groups represented by R<sub>6</sub> and/or R<sub>7</sub> by hydrogen atoms under the conditions described above.

Generally, the action of activated Raney nickel in the presence of an aliphatic alcohol or an ether is performed at a temperature of from -10° to 60° C.

According to the invention, the product of general formula (XXI) in which Z<sub>1</sub> and R<sub>4</sub> are defined as above may be obtained by the action of a sulfoxide of general formula (XXIV):



in which R' and R'' are defined as above, on a product of general formula (XIX).

Generally, the reaction of the sulfoxide of general formula (XXIV), preferably dimethyl sulfoxide, with the product of general formula (XIX) is performed in the presence of a mixture of acetic acid and acetic anhydride or a derivative of acetic acid such as a haloacetic acid at a temperature of from 0° to 50° C., and preferably at about 25° C.

The new products of general formula (I) obtained by carrying out the processes according to the invention may be purified according to known methods such as crystallization or chromatography.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy biological properties.

In vitro, measurement of the biological activity is performed on tubulin extracted from pig's brain by the method of M. L. Shelanski et al., Proc. Natl. Acad. Sci. USA, 70, 765–768 (1973). Study of the depolymerization of microtubules to tubulin is performed according to the method of G. Chauvière et al., C.R. Acad. Sci., 293, series II, 501–503 (1981). In this study, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be at least as active as taxol and Taxotere.

In vivo, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be active in mice grafted with B16 melanoma at doses of from 1 to 30 mg/kg administered intraperitoneally, as well as on other liquid or solid tumours.

The new products have antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®. Such tumours comprise colon tumours which have a high expression of the mdr 1 gene (multiple drug resistance gene). Multiple drug resistance is a customary term relating to the resistance of a tumour to different products having different structures and mechanisms of action. Taxoids are generally known to be strongly recognized by experimental tumours such as P388/DOX, a

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raphy [12 Merck preparative silica gel 60F<sub>254</sub> plates, thickness 1 mm, application in solution in a methanol/dichloromethane (5:95 by volume) mixture, eluting with a methanol/dichloromethane (5:95 by volume) mixture]. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through sintered glass and evaporation of the solvents under reduced pressure (0.27 kPa) at a temperature in the region of 40° C., 126 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2 R, 3 S)-3-tert-butoxycarbonylamo-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

optical rotation  $[\alpha]_{D}^{20} = -32.9$  (c=0.5; methanol)

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: CH<sub>3</sub>); 1.25 (s, 3H: CH<sub>3</sub>); 1.39 (s, 9H: C(CH<sub>3</sub>)<sub>3</sub>); 1.70 (s, 1H: OH at position 1); 1.75 (s, 3H: CH<sub>3</sub>); 1.82 and 2.72 (2 mts, 1H each: CH<sub>2</sub> at position 6); 1.91 (s, 3H: CH<sub>3</sub>); 2.31 (limiting AB, 2H: CH<sub>2</sub> at position 14); 2.39 (s, 3H: COCH<sub>3</sub>); 3.33 and 3.48 (2 s, 3H each: OCH<sub>3</sub>); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: H 3); 3.88 (dd, J=11 and 7, 1H: H 7); 4.20 and 4.33 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.65 (mt, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 5.00 (broad d, J=10, 1H: H at position 5); 5.30 (broad d, J=10, 11H: H at position 3'); 5.47 (d, J=10, 1H: CONH); 5.66 (d, J=7, 1H: H at position 2); 6.24 (broad t, J=9, 1H: H at position 13); from 7.30 to 7.50 (mt, 5H: aromatic H at position 3'); 7.52 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.63 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.12 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene (or 7β,10β-dimethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

86 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 500 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene in 5 cm<sup>3</sup> of iodomethane and 0.5 cm<sup>3</sup> of dimethylformamide. After 45 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 50 cm<sup>3</sup> of ethyl acetate and 8 cm<sup>3</sup> of distilled water. After settling had taken place, the organic phase was separated and washed with twice 8 cm<sup>3</sup> of distilled water and then 8 cm<sup>3</sup> of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 570 mg of a pale yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 10-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 1.97 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub>; with a few drops of CD<sub>3</sub>OD-d<sub>4</sub>, chemical shifts δ in ppm; coupling constants J in Hz): 1.03 (s, 3H: CH<sub>3</sub>); 1.11 (s, 3H: CH<sub>3</sub>); 1.65 (s, 3H:

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CH<sub>3</sub>); 1.72 and 2.67 (2 mts, 1H each: CH<sub>2</sub> at position 6); 2.05 (s, 3H: CH<sub>3</sub>); 2.21 (limiting AB, J=14 and 9, 2H: CH<sub>2</sub> at position 14); 2.25 (s, 3H: COCH<sub>3</sub>); 3.26 and 3.40 (2 s, 3H each: OCH<sub>3</sub>); 3.85 (d, J=7, 1H: H at position 3); 3.89 (dd, J=11 and 6.5, 1H: H at position 7); 4.12 and 4.25 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.78 (broad t, J=9, 1H: H at position 13); 4.83 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.53 (d, J=7, 1H: H at position 2); 7.43 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.56 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.05 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene (or 10β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

50 cm<sup>3</sup> of hydrogen fluoride/triethylamine complex (3HF.Et<sub>3</sub>N) were added slowly to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 30 cm<sup>3</sup> of dichloromethane. After 48 hours at a temperature in the region of 20° C., the reaction mixture was poured into a suspension of 100 cm<sup>3</sup> of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After settling had taken place, the aqueous phase was separated and re-extracted with three times 80 cm<sup>3</sup> of dichloromethane and then twice 80 cm<sup>3</sup> of ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 3.45 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with a methanol/dichloromethane (5:95 by volume) mixture and collecting 35-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 1.97 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm; coupling constants J in Hz): 1.10 (s, 3H: CH<sub>3</sub>); 1.19 (s, 3H: CH<sub>3</sub>); 1.48 (d, J=8.5, 1H: OH at position 13); 1.70 (s, 3H: CH<sub>3</sub>); 1.81 and 2.61 (2 mts, 1H each: CH<sub>2</sub> at position 6); 2.09 (d, J=5, 1H: OH at position 7); 2.11 (s, 3H: CH<sub>3</sub>); 2.30 (s, 3H: COCH<sub>3</sub>); 2.32 (d, J=9, 2H: CH<sub>2</sub> at position 14); 3.48 (s, 3H: OCH<sub>3</sub>); 3.97 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.31 (mt, 1H: H at position 7); 4.93 (mt, 1H: H at position 13); 4.99 (s, 1H: H at position 10); 5.01 (broad d, J=10, 1H: H at position 5); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.63 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.12 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-methoxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

375 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 5 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-

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bis(triethylsilyloxy)-11-taxene in 25 cm<sup>3</sup> of iodomethane. The solution was stirred constantly for 45 minutes at a temperature in the region of 0° C., and then for 5 hours 30 minutes at a temperature in the region of 20° C. The reaction mixture was cooled again to a temperature in the region of 0° C., and 125 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise. After 1 hour at 20° C. and then 18 hours at 5° C., the reaction mixture was diluted by adding 50 cm<sup>3</sup> of dichloromethane and poured into 50 cm<sup>3</sup> of saturated aqueous ammonium chloride solution, and settling was allowed to take place. The aqueous phase was separated and extracted with twice 30 cm<sup>3</sup> of dichloroemethane, and the organic phases were then combined, washed with 10 cm<sup>3</sup> of distilled water, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 5.15 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 300 g of silica (0.063–0.2 mm) contained in a column 5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 10:90 by volume), collecting 30-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (600 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm; coupling constants J in Hz): 0.58 and 0.69 (2 mts, 6H each: ethyl CH<sub>2</sub>); 0.97 and 1.04 (2 t, J=7.5, 9H each: ethyl CH<sub>3</sub>); 1.15 (s, 3H: CH<sub>3</sub>); 1.18 (s, 3H: CH<sub>3</sub>); 1.58 (s, 1H: OH at position 1); 1.68 (s, 3H: CH<sub>3</sub>); 1.89 and 2.48 (2 mts, 1H each: CH<sub>2</sub> at position 6); 2.04 (s, 3H: CH<sub>3</sub>); 2.15 and 2.23 (2 dd, J=16 and 9, 1H each: CH<sub>2</sub> at position 14); 2.29 (s, 3H: COCH<sub>3</sub>); 3.40 (s, 3H: OCH<sub>3</sub>); 3.83 (d, J=7, 1H: H at position 13); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.43 (dd, J=11 and 7, 1H: H at position 7); 4.91 (s 1H: H at position 10); 4.96 (broad d, J=10, 1H at position 5); 5.01 (broad t, J=9, 1H: H at position 13); 5.62 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.60 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.09 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10-deacetyl-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

10.8 cm<sup>3</sup> of triethylsilyl chloride were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 14 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β,13α-tetrahydroxy-9-oxo-11-taxene (10-deacetyl baccatin III) in 50 cm<sup>3</sup> of anhydrous pyridine. After 17 hours at a temperature in the region of 20° C., the reaction mixture was brought to a temperature in the region of 115° C. and 10.8 cm<sup>3</sup> of triethylsilyl chloride were then added. After 3 hours 15 minutes at a temperature in the region of 115° C., the reaction mixture was brought back to a temperature in the region of 20° C. and diluted with 30 cm<sup>3</sup> of ethyl acetate and 100 cm<sup>3</sup> of distilled water. After settling took place, the aqueous phase was separated and extracted with twice 50 cm<sup>3</sup> of ethyl acetate. The organic phases were combined, washed with 50 cm<sup>3</sup> of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the

region of 40° C. 63.1 g of a brown oil were thereby obtained, which product was purified by chromatography at atmospheric pressure on 800 g of silica (0.063–0.2 mm) contained in a column 7 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 5:95 by volume), collecting 60-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 9.77 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a cream-coloured foam, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm; coupling constants J in Hz): 0.55 and 0.68 (2 mts, 6H each: ethyl CH<sub>2</sub>); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl CH<sub>3</sub>); 1.08 (s, 3H: CH<sub>3</sub>); 1.17 (s, 3H: CH<sub>3</sub>); 1.58 (s, 1H: OH at position 1); 1.73 (s, 3H: CH<sub>3</sub>); 1.91 and 2.57 (2 mts, 1H each: CH<sub>2</sub> at position 2); 2.04 (s, 3H: CH<sub>3</sub>); 2.12 and 2.23 (2 dd, J=16 and 9, 1H each: CH<sub>2</sub> at position 14); 2.30 (s, 3H: COCH<sub>3</sub>); 3.88 (d, J=7, 1H: H at position 3); 4.16 and 4.32 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.27 (d, J=1, 1H: OH at position 10); 4.40 (dd, J=11 and 7, 1H: H at position 7); 4.95 (broad d, J=10, 1H: H at position 5); 4.95 (mt, 1H: H at position 13); 5.16 (d, J=1, 1H: H at position 10); 5.60 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.60 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.09 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

**EXAMPLE 2**

340 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were dissolved in 8 cm<sup>3</sup> of a 0.1N ethanolic solution of hydrochloric acid containing 1% of water. The solution thereby obtained was stirred for 13 hours at a temperature in the region of 20° C. and then for 80 hours at 4° C., and 20 cm<sup>3</sup> of dichloromethane were added. The organic phase was separated after settling had taken place and washed successively with 3 times 5 cm<sup>3</sup> of saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 300 mg of a white foam were obtained, which product was purified by chromatography on silica gel deposited on plates [gel 1 mm thick, plates is 20×20 cm, eluent: dichloromethane/methanol (95:5 by volume)] in 80-mg fractions (4 plates). After localization with UV rays of the zone corresponding to the adsorbed desired product, this zone was scraped off, and the silica collected was washed on sintered glass with 10 times 5 cm<sup>3</sup> of ethyl acetate. The filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. A white foam was obtained, which was repurified according to the same technique [3 plates; 20×20×1 mm; eluent: dichloromethane/ethyl acetate (90:10 by volume)]. 205 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were thereby obtained in the form of a white foam, the characteristics of which were as follows:

optical rotation:  $[\alpha]_{D}^{20} = -33$  (c=0.5; methanol).

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: —CH<sub>3</sub>); 1.25 (s, 3H: —CH<sub>3</sub>); 1.39 [s, 9H: —C(CH<sub>3</sub>)<sub>3</sub>]; 1.70 (s, 1H: —OH at position 1); 1.75 (s, 3H: —CH<sub>3</sub>); 1.82 and 2.72 (2 mts, 1H each: —CH<sub>2</sub> at position 6); 1.91 (s, 3H: —CH<sub>3</sub>);

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2.31 (limiting AB, 2H: —CH<sub>2</sub> at position 14); 2.39 (s, 3H: —COCH<sub>3</sub>); 3.33 and 3.48 (2 s, 3H each: —OCH<sub>3</sub>); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: —H at position 3); 3.88 (dd, J=11 and 7, 1H: —H at position 7); 4.20 and 4.33 (2d, J=8.5, 1H each: —CH<sub>2</sub> at position 20); 4.65 (mt, 1H: —H at position 2'); 4.83 (s, 1H: —H at position 10); 5.00 (broad d, J=10, 1H: —H at position 5); 5.30 (broad d, J=10, 1H: —H at position 3'); 5.47 (d, J=10, 1H: —CONH—); 5.66 (d, J=7, 1H: —H at position 2); 6.24 (broad t, J=9, 1H: —H at position 13); from 7.30 to 7.50 (mt, 5H: —C<sub>6</sub>H<sub>5</sub> at position 3'); 7.52 [t, J=7.5, 2H: —OCOC<sub>8</sub>H<sub>5</sub> (—H at position 3 and H at position 5)]; 7.63 [t, J=7.5, 1H: —OCOC<sub>8</sub>H<sub>5</sub> (—H at position 4)]; 8.12 [d, J=7.5, 2H: —OCOC<sub>8</sub>H<sub>5</sub> (—H at position 2 and H at position 6)].

4 $\alpha$ -Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

100 cm<sup>3</sup> of an ethanolic suspension of activated nickel according to Raney (obtained from 80 cm<sup>3</sup> of the approximately 50% commercial aqueous suspension by successive washing, to a pH in the region of 7, with 15 times 100 cm<sup>3</sup> of distilled water and with 5 times 100 cm<sup>3</sup> of ethanol) were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 1 g of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -bis(methylthiomethoxy)-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 100 cm<sup>3</sup> of anhydrous ethanol. The reaction medium was kept stirring for 24 hours at a temperature in the region of 20° C. and then filtered through sintered glass. The sintered glass was washed with 4 times 80 cm<sup>3</sup> of ethanol, and the filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 710 mg of a yellow foam were obtained, which product was purified by chromatography on 60 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter [eluent: dichloromethane/ethyl acetate (90:10 by volume)], collecting 6-cm<sup>3</sup> fractions. Fractions containing only the desired product are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 350 mg of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4 $\alpha$ -Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -bis(methylthiomethoxy)-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

2.3 cm<sup>3</sup> of acetic acid and 7.55 cm<sup>3</sup> of acetic anhydride were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 3.1 g of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ ,7 $\beta$ ,10 $\beta$ -trihydroxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate dissolved in 102 cm<sup>3</sup> of dimethyl sulphoxide. The reaction mixture was kept stirring for 7 days at a temperature in the region of 20° C., and then poured into a mixture of 500 cm<sup>3</sup> of distilled water and 250 cm<sup>3</sup> of dichloromethane. 30 cm<sup>3</sup> of saturated aqueous potassium carbonate solution were then added with efficient stirring to a pH in the region of 7. After 10 minutes of stirring, the organic phase was separated after settling had taken place and the aqueous phase was re-extracted with

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twice 250 cm<sup>3</sup> of dichloromethane. The organic phases were combined, washed with 250 cm<sup>3</sup> of distilled water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 5.2 g of a pale yellow oil were obtained, which product was purified by chromatography on 200 g of silica (0.063–0.4 mm) contained in a column 3 cm in diameter [eluent: dichloromethane/methanol (99:1 by volume)], collecting 50-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 1.25 g of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -bis(methylthiomethoxy)-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4 $\alpha$ -Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ ,7 $\beta$ ,10 $\beta$ -trihydroxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

A solution of 5.1 g of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-9-oxo-7 $\beta$ ,10 $\beta$ -bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in a mixture of 100 cm<sup>3</sup> of methanol and 100 cm<sup>3</sup> of acetic acid was heated, with stirring and under an argon atmosphere, to a temperature in the region of 60° C., and 10 g of powdered zinc were then added. The reaction mixture was then stirred for 15 minutes at 60° C., thereafter cooled to a temperature in the region of 20° C. and filtered through sintered glass lined with Celite. The sintered glass was washed with twice 15 cm<sup>3</sup> of methanol. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 50 cm<sup>3</sup> of ethyl acetate and 25 cm<sup>3</sup> of saturated aqueous sodium hydrogen carbonate solution were added to the residue. The organic phase was separated after settling had taken place and washed successively with 25 cm<sup>3</sup> of saturated aqueous sodium hydrogen carbonate solution and with 25 cm<sup>3</sup> of distilled water, then dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 3.1 g of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ ,7 $\beta$ ,10 $\beta$ -trihydroxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4 $\alpha$ -Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-9-oxo-7 $\beta$ ,10 $\beta$ -bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared under the conditions described in Patent WO 94/07878, the disclosure of which is specifically incorporated by reference herein.

**EXAMPLE 3**

76 mg of dicyclohexylcarbodiimide and then 8.5 mg of 4-N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 135 mg of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-10 $\beta$ -ethoxy-1 $\beta$ ,13 $\alpha$ -dihydroxy-7 $\beta$ -methoxy-9-oxo-11-taxene, 120 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 1 cm<sup>3</sup> of anhydrous toluene. The suspension obtained was stirred at

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a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 320.6 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel 60F<sub>254</sub> plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 47.7 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were obtained in the form of a cream-coloured solid and 37 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which 5-carboxylate product were as follows:

<sup>1</sup>H NMR spectrum (600 MHz; CDCl<sub>3</sub>; at a temperature of 333 K; chemical shifts δ in ppm; coupling constants J in Hz): 1.09 (s, 9H: C(CH<sub>3</sub>)<sub>3</sub>); 1.19 (s, 3H: CH<sub>3</sub>); 1.21 (s, 3H: CH<sub>3</sub>); 1.27 (t, J=7, 3H: ethyl CH<sub>3</sub>); 1.43 (s, 1H: OH at position 1); 1.62 (s, 3H: CH<sub>3</sub>); 1.68 (s, 3H: CH<sub>3</sub>); 1.77 and 2.63 (2 mts, 1H each: CH<sub>2</sub> at position 6); 1.86 (s, 3H: COCH<sub>3</sub>); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: CH<sub>2</sub> at position 14); 3.27 (s, 3H: OCH<sub>3</sub>); 3.45 and 3.68 (2 mts, 1H each: ethyl CH<sub>2</sub>); 3.76 (d, J=7, 1H: H3); 3.81 (s, 3H: ArOCH<sub>3</sub>); 3.85 (dd, J=11 and 7, 1H: H at position 7); 4.13 and 4.23 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.58 (d, J=4.5, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.46 (d, J=4.5, 1H: H at position 3'); 5.60 (d, J=7 Hz, 1H: H2); 6.13 (broad t, J=9 Hz, 1H: H13); 6.38 (s, 1H: H5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to OCH<sub>3</sub>); from 7.30 to 7.50 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to OCH<sub>3</sub> and OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.59 (t, J=7.5, 1H: OCOC<sub>8</sub>H<sub>5</sub> H at the para position); 8.03 (d, J=7.5, 2H: OCOC<sub>8</sub>H<sub>5</sub> H at the ortho position).

A solution of 48 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.5 cm<sup>3</sup> of ethyl acetate and 0.004 cm<sup>3</sup> of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1.5 hours under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 5 Merck preparative silica gel 60F<sub>254</sub> plates, thickness 0.5 mm, eluting with a methanol/dichloromethane (4:96 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 28.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-

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11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm; coupling constants J in Hz): 1.22 (s, 3H: CH<sub>3</sub>); 1.25 (s, 3H: CH<sub>3</sub>); 1.32 (t, J=7, 3H: ethyl CH<sub>3</sub>); 1.38 (s, 9H: C(CH<sub>3</sub>)<sub>3</sub>); 1.64 (s, 1H: OH at position 1); 1.73 (s, 3H: CH<sub>3</sub>); 1.80 and 2.70 (2 mts, 1H each: CH<sub>2</sub> at position 6); 1.88 (s, 3H: CH<sub>3</sub>); 2.30 (mt, 2H: CH<sub>2</sub> at position 14); 2.38 (s, 3H: COCH<sub>3</sub>); 3.31 (s, 3H: OCH<sub>3</sub>); 3.44 (unres. comp., 1H: OH at position 2'); 3.50 and 3.70 (2 mts, 1H each ethyl OCH<sub>2</sub>); 3.84 (d, J=7.5, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.32 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.64 (mt, 1H: H at position 2'); 4.90 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.62 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.12 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-ethoxy-7β-methoxy-10-deacetoxybaccatin III) may be prepared in the following manner:

43 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 235 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene in 2.5 cm<sup>3</sup> of iodomethane and 1 cm<sup>3</sup> of dimethylformamide. After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 cm<sup>3</sup> of ethyl acetate, 6 cm<sup>3</sup> of distilled water and 8 cm<sup>3</sup> of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 8 cm<sup>3</sup> of distilled water and then 8 cm<sup>3</sup> of saturated aqueous NaCl solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 268 mg of a yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene are thereby obtained in the form of a white powder, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (300 MHz; CDCl<sub>3</sub> with the addition of a few drops of CD<sub>3</sub>OD-d<sub>4</sub>; chemical shifts δ in ppm, coupling constants J in Hz): 0.99 (s, 3H: CH<sub>3</sub>); 1.09 (s, 3H: CH<sub>3</sub>); 1.22 (t, J=7, 3H: ethyl CH<sub>3</sub>); 1.62 (s, 3H: CH<sub>3</sub>); 1.68 and 2.66 (2 mts, 1H each: CH<sub>2</sub>6); 2.03 (s, 3H, CH<sub>3</sub>); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: CH<sub>2</sub> at position 14); 2.23 (s, 3H: COCH<sub>3</sub>); 3.23 (s, 3H: OCH<sub>3</sub>); from 3.40 to 3.65 (mt, 2H: ethyl CH<sub>2</sub>); 3.84 (d, J=7.5, 1H: H at position 3'); 3.88 (dd, J=10 and 6.5, 1H: H at position 7); 4.10 and 4.23 (2 d, J=8.5, 1H each: CH<sub>2</sub> 20); 4.75 (broad t, J=9, 1H: H at position 13); 4.90 (s, 1H: H at position 10); 4.97 (broad d, J=10, 1H: H at position 5); 5.51 (d, J=7.5, 1H: H at position 2); 7.42 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position);

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7.53 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> at the para position); 8.03 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene (or 10β-ethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

9 cm<sup>3</sup> of hydrogen fluoride/triethylamine complex (3HF.Et<sub>3</sub>N) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 591 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β, hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 6 cm<sup>3</sup> of dichloromethane. After 21 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 40 cm<sup>3</sup> of dichloromethane and poured into a suspension of 40 cm<sup>3</sup> of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 cm<sup>3</sup> of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm<sup>3</sup> of diethyl ether. The organic phases were combined, washed with 20 cm<sup>3</sup> of distilled water and 20 cm<sup>3</sup> of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 370 mg of a pale yellow foam were thereby obtained, which product is purified by chromatography at atmospheric pressure on 35 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 236.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm, coupling constants J in Hz): 1.08 (s, 3H: CH<sub>3</sub>); 1.19 (s, 3H: CH<sub>3</sub>); 1.29 (t, J=7.5, 3H: ethyl CH<sub>3</sub>); 1.38 (d, J=9, 1H: OH at position 7); 1.59 (s, 1H: OH at position 1); 1.69 (s, 3H: CH<sub>3</sub>); 1.82 and 2.62 (2 mts, 1H each: CH<sub>2</sub> at position 6); 2.02 (d, J=5, 1H: OH at position 13); 2.08 (s, 3H: CH<sub>3</sub>); 2.30 (s, 3H: COCH<sub>3</sub>); 2.32 (d, J=9, 2H: CH<sub>2</sub> at position 14); 3.56 and 3.67 (2 mts, 1H each: ethyl OCH<sub>2</sub>); 3.98 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5 Hz, 1H each: CH<sub>2</sub>20); 4.30 (mt, 1H: H7); 4.90 (mt, 1H: H at position 13); 4.99 (dd, J=10 and 1.5, 1H: H at position 5); 5.05 (s, 1H: H at position 10); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.63 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.12 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-ethoxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight of liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm<sup>3</sup> of iodoethane and 4 cm<sup>3</sup> of dimethylformamide. The solution was kept stirring for 17 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin was then added portionwise. After 50 minutes at a temperature in the region of 20° C., the reaction

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mixture was diluted with 100 cm<sup>3</sup> of ethyl acetate and 10 cm<sup>3</sup> of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm<sup>3</sup> of distilled water and then 10 cm<sup>3</sup> of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.2 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm<sup>3</sup> fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 379.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 430 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a white foam, the characteristics of which 10-β-ethoxy product were as follows:

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>; chemical shifts δ in ppm, coupling constants J in Hz): 0.57 and 0.70 (2 mts, 6H each; ethyl CH<sub>2</sub>); 0.97 and 1.03 (2 t, J=7.5, 9H each: ethyl CH<sub>3</sub>); 1.13 (s, 3H: CH<sub>3</sub>); 1.20 (s, 3H: CH<sub>3</sub>); 1.29 (t, J=7.5, 3H: CH<sub>3</sub> of ethoxy at position 10); 1.58 (s, 1H: OH at position 1); 1.66 (s, 3H: CH<sub>3</sub>); 1.89 and 2.58 (2 mts, 1H each: CH<sub>2</sub> at position 2); 2.03 (s, 3H: CH<sub>3</sub>); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each CH<sub>2</sub> at position 14); 2.30 (s, 3H: COCH<sub>3</sub>); 3.53 (mt, 2H: CH<sub>2</sub> of ethoxy at position 10); 3.84 (d, J=7, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.43 (dd, J=11 and 6.5, 1H: H at position 7); from 4.90 to 5.00 (mt, 2H: H at position 13 and H at position 5), 5.01 (s, 1H: H at position 10); 5.61 (d, J=7, 1H: H at position 2); 7.48 (t, J=7.5, 2H: OCOC<sub>8</sub>H<sub>5</sub> H at the meta position); 7.61 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.10 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

## EXAMPLE 4

65 mg of dicyclohexylcarbodiimide and then 7 mg of 4-(N,N-dimethylaminopyridine were added successively at a temperature in the region of 20° C. to a suspension containing 115 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene and 100 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid in 1 cm<sup>3</sup> of anhydrous toluene. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 276.2 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel 60F<sub>254</sub> plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through

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cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 84.8 mg of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-10 $\beta$ -(1-propyl)oxy-1 $\beta$ -hydroxy-7 $\beta$ -methoxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which were as follows:

$^1$ H NMR spectrum (300 MHz; CDCl<sub>3</sub>; chemical shifts  $\delta$  in ppm; coupling constants J in Hz): 0.97 (t, J=7, 3H: propyl CH<sub>3</sub>); 1.07 (s, 9H: C(CH<sub>3</sub>)<sub>3</sub>); 1.19 (s, 6H: CH<sub>3</sub>); from 1.50 to 1.80 (mt, 3H: OH at position 1 and central CH<sub>2</sub> of propyl); 1.60 (s, 3H: CH<sub>3</sub>); 1.70 (s, 3H: CH<sub>3</sub>); 1.78 and 2.63 (2 mts, 1H each: CH<sub>2</sub> at position 6); 1.82 (unres. comp. 3H: COCH<sub>3</sub>); 2.07 and 2.19 (2 dd, J=16 and 9, 1H each: CH<sub>2</sub> at position 14); 3.26 (s, 3H: OCH<sub>3</sub>); 3.30 and 3.58 (2 mts, 1H each: propyl OCH<sub>2</sub>); 3.73 (d, J=7.5, 1H: H at position 3); 3.81 (s, 3H: ArOCH<sub>3</sub>); 3.81 (mt, 1H: H at position 7); 4.09 and 4.23 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.57 (d, J=4.5, 1H: H at position 2'); 4.79 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.40 (unres. comp. 1H: H at position 3'); 5.58 (d, J=7.5, 1H: H at position 2); 6.13 (broad t, J=9, 1H: H at position 13); 6.40 (spread unres. comp 1H: H at position 5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to OCH<sub>3</sub>); from 7.30 to 7.60 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to OCH<sub>3</sub> and OCOC<sub>6</sub>H<sub>5</sub> meta H); 7.63 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.03 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4 $\alpha$ -Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-10 $\beta$ -(1-propyl)oxy-1 $\beta$ -hydroxy-7 $\beta$ -methoxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate was prepared in the following manner:

A solution of 84 mg of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-10 $\beta$ -(1-propyl)oxy-1 $\beta$ -hydroxy-7 $\beta$ -methoxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.84 cm<sup>3</sup> of ethyl acetate and 0.0071 cm<sup>3</sup> of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1 hour under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 6 Merck preparative silica gel 60F<sub>254</sub> plates, thickness 0.5 mm, eluting with a methanol/acetonitrile/dichloromethane (3:7:90 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 27 mg of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-10 $\beta$ -(1-propyl)oxy-1 $\beta$ -hydroxy-7 $\beta$ -methoxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of a white foam, the characteristics of which are as follows:

$^1$ H NMR spectrum (400 MHz; CDCl<sub>3</sub>; chemical shifts  $\delta$  in ppm; coupling constants J in Hz): 0.99 (t, J=7, 3H: propyl CH<sub>3</sub>); 1.22 (s, 3H: CH<sub>3</sub>); 1.25 (s, 3H: CH<sub>3</sub>); 1.38 (s, 9H: C(CH<sub>3</sub>)<sub>3</sub>); 1.64 (s, 1H: OH at position 1); 1.69 (mt, 2H: central CH<sub>2</sub> of propyl); 1.73 (s, 3H: CH<sub>3</sub>); 1.80 and 2.70 (2 mts, 1H each: CH<sub>2</sub> at position 6); 1.88 (s, 3H: CH<sub>3</sub>); 2.30 (mt, 2H: CH<sub>2</sub> at position 14); 2.38 (s, 3H: COCH<sub>3</sub>); 3.31 (s, 3H: OCH<sub>3</sub>); 3.36 and 3.64 (2 mts, 1H each: propyl OCH<sub>2</sub>); 3.44 (unres. comp. 1H: OH at position 2'); 3.84 (d, J=7.5, Hz, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.30 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.64 (mt, 1H: H at position 2'); 4.89 (s, 1H: H

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at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.61 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.12 (d, J=7.5, 2H: OCOC<sub>8</sub>H<sub>5</sub> H at the ortho position).

4 $\alpha$ -Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-10 $\beta$ -(1-propyl)oxy-1 $\beta$ ,13 $\alpha$ -dihydroxy-7 $\beta$ -methoxy-9-oxo-11-taxene (or 10 $\beta$ -(1-propyl)oxy-7 $\beta$ -methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

30 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 165 mg of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ ,7 $\beta$ ,13 $\alpha$ -trihydroxy-10 $\beta$ -(1-propyl)oxy-9-oxo-11-taxene in 1.7 cm<sup>3</sup> of iodomethane and 1 cm<sup>3</sup> of dimethylformamide. After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 cm<sup>3</sup> of ethyl acetate, 5 cm<sup>3</sup> of distilled water and 7 cm<sup>3</sup> of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 7 cm<sup>3</sup> of distilled water and then 7 cm<sup>3</sup> of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C.

224 mg of the yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 20 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 117.5 mg of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-10 $\beta$ -(1-propyl)oxy-1 $\beta$ ,13 $\alpha$ -dihydroxy-7 $\beta$ -methoxy-9-oxo-11-taxene were thereby obtained in the form of a white foam, the characteristics of which were as follows:

$^1$ H NMR spectrum (300 MHz; CDCl<sub>3</sub>; chemical shifts  $\delta$  in ppm, coupling constants J in Hz): 0.98 (t, J=7, 3H: propyl CH<sub>3</sub>); 1.05 (s, 3H: CH<sub>3</sub>), 1.19 (s, 3H: CH<sub>3</sub>); from 1.60 to 1.80 (mt, 2H: central CH<sub>2</sub> of propyl); from 1.65 to 1.85 and 2.66 (2 mts, 1H each: CH<sub>2</sub> at position 6); 1.72 (s, 3H: CH<sub>3</sub>); 2.10 (s, 3H: CH<sub>3</sub>); from 2.05 to 2.35 (mt, 2H: CH<sub>2</sub> at position 14); 2.28 (s, 3H: COCH<sub>3</sub>); 3.32 (s, 3H: OCH<sub>3</sub>); 3.45 and 3.65 (2 mts, 1H each: propyl OCH<sub>2</sub>); 3.92 (d, J=7.5, 1H: H3); 3.93 (dd, J=11 and 6, 1H: H at position 7); 4.16 and 4.32 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.90 (mt, 1H: H at position 13); 4.94 (s, 1H: H at position 10); 5.03 (broad d, J=10, 1H: H at position 5); 5.60 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.62 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.11 (d, J=7.5, 2H: OCOC<sub>8</sub>H<sub>5</sub> H at the ortho position).

4 $\alpha$ -Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ ,7 $\beta$ ,13 $\alpha$ -trihydroxy-10 $\beta$ -(1-propyl)oxy-9-oxo-11-taxene (or 10 $\beta$ -(1-propyl)oxy-10-deacetoxybaccatin III) was prepared in the following manner:

8.75 cm<sup>3</sup> of hydrogen fluoride/triethylamine complex (3HF.Et<sub>3</sub>N) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 585 mg of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-10 $\beta$ -(1-propyl)oxy-9-oxo-7 $\beta$ ,13 $\alpha$ -bis

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(triethylsilyloxy)-11-taxene in 6 cm<sup>3</sup> of dichloromethane. After 24 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 30 cm<sup>3</sup> of dichloromethane and poured into a suspension of 30 cm<sup>3</sup> of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 cm<sup>3</sup> of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm<sup>3</sup> of diethyl ether. The organic phases were combined, washed with 20 cm<sup>3</sup> of distilled water and 20 cm<sup>3</sup> of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 500 mg of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 40 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm<sup>3</sup> fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 373.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (300 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm, coupling constants J in Hz): 0.95 (t, J=7, 3H: propyl CH<sub>3</sub>); 1.06 (s, 3H: CH<sub>3</sub>); 1.22 (s, 3H: CH<sub>3</sub>); 1.45 (d, J=7.5, 1H: OH at position 7); from 1.60 to 1.80 (mt, 2H: central CH<sub>2</sub> of propyl); 1.67 (s, 3H: CH<sub>3</sub>); 1.83 and 2.62 (2 mts, 1H each: CH<sub>2</sub> at position 6); 2.05 (s, 3H: CH<sub>3</sub>); 2.05 (mt, 1H: OH at position 13); 2.27 (limiting AB, 2H: CH<sub>2</sub> at position 4); 2.28 (s, 3H: COCH<sub>3</sub>); 3.40 and 3.57 (2 mts, 1H each: propyl OCH<sub>2</sub>); 3.97 (d, J=7.5, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.28 (mt, 1H: H at position 7); 4.90 (mt, 1H: H at position 13); 4.98 (broad d, J=10, 1H: H at position 5); 5.03 (s, 1H: H at position 10); 5.65 (d, J=7.5, 1H: H at position 2); 7.50 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.60 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.00 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm<sup>3</sup> of iodoethane and 4 cm<sup>3</sup> of dimethylformamide. The solution was kept stirring for 19 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were then added portionwise. After 3 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 100 cm<sup>3</sup> of ethyl acetate and 10 cm<sup>3</sup> of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm<sup>3</sup> of distilled water and then 10 cm<sup>3</sup> of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.32 g of a pale yellow foam were thereby obtained, which product was purified by

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chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm<sup>3</sup> fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 376.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 395.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

<sup>1</sup>H NMR spectrum (400 MHz; CDCl<sub>3</sub>; chemical shifts δ in ppm, coupling constants J in Hz); 0.57 and 0.70 (2 mts, 6H each: ethyl CH<sub>2</sub>); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl CH<sub>3</sub>); 0.94 (t, J=7.5, 3H: propyl CH<sub>3</sub>); 1.14 (s, 3H: CH<sub>3</sub>); 1.21 (s, 3H: CH<sub>3</sub>); 1.67 (s, 3H: CH<sub>3</sub>); 1.69 (mt, 2H: central CH<sub>2</sub> of propyl); 1.88 and 2.48 (2 mts, 1H each: CH<sub>2</sub> at position 6); 2.03 (s, 3H: CH<sub>3</sub>); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each: CH<sub>2</sub> at position 14); 2.30 (s, 3H: COCH<sub>3</sub>); 3.40 (mt, 2H: propyl OCH<sub>2</sub>); 3.84 (d, J=7.5, 1H: H at position 3); 4.16 and 4.30 (2 d, J=8.5, 1H each: CH<sub>2</sub> at position 20); 4.44 (dd, J=11 and 6.5, 1H: H at position 7); 4.96 (broad d, J=10 Hz, 1H: H5); 4.97 (s, 1H: H 10), 4.99 (broad t, J=9 Hz, 1H: H at position 13); 5.62 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the meta position); 7.60 (t, J=7.5, 1H: OCOC<sub>6</sub>H<sub>5</sub> H at the para position); 8.10 (d, J=7.5, 2H: OCOC<sub>6</sub>H<sub>5</sub> H at the ortho position).

The new products of general formula (I) in which Z represents a radical of general formula (II) manifest significant inhibitory activity with respect to abnormal cell proliferation, and possess therapeutic properties permitting the treatment of patients having pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cell proliferation of malignant or non-malignant cells of various tissues and/or organs, comprising, without implied limitation, muscle, bone or connective tissue, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive system, pancreas and thyroid or adrenal glands. These pathological conditions can also include psoriasis, solid tumours, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanoma, multiple myeloma, chronic lymphocytic leukaemia and acute or chronic granulocytic lymphoma.

The new products according to the invention are especially useful for the treatment of cancer of the ovary. The products according to the invention may be used to prevent or delay the appearance or reappearance of the pathological conditions, or to treat these pathological conditions.

The products according to the invention may be administered to a patient according to different dosage forms suited to the chosen administration route, which is preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administration. Intraperitoneal or intravenous administration is more especially preferred.

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The compositions may be prepared

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according to the customary methods, using one or more pharmaceutically acceptable adjuvants, vehicles or excipients. Suitable vehicles include diluents, sterile aqueous media and various non-toxic solvents. Preferably, the compositions take the form of aqueous solutions or suspensions, injectable solutions which can contain emulsifying agents, colourings, preservatives or stabilizers. However, the compositions can also take the form of tablets, pills, powders or granules which can be administered orally.

The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

For parenteral administration, sterile, aqueous or non-aqueous solutions or suspensions are used. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum, or injectable organic esters such as ethyl oleate, may be used. The sterile aqueous solutions can consist of a solution of a pharmaceutically acceptable salt dissolved in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition.

It is clearly understood that all the products participating in the compositions according to the invention must be pure and non-toxic in the amounts used.

The compositions can contain at least 0.01% of therapeutically active product. The amount of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared in such a way that a single dose contains from 0.01 to 1000 mg approximately of active product for parenteral administration.

The therapeutic treatment may be performed concurrently with other therapeutic treatments including antineoplastic drugs, monoclonal antibodies, immunotherapy or radiotherapy or biological response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons ( $\alpha$ ,  $\beta$  or  $\delta$ ) and TNF.

Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents, for instance nitrogen mustards such as mechlorethamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine, lomustine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues, for instance methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products, for instance vinca alkaloids such as vinblastine, vincristine and vindesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum, for instance cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocortical suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and

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ethynodiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

5 The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the administration form, the particular product selected and features distinctive to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders due to abnormal cell proliferation.

10 15 The products according to the invention may be administered as often as necessary to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary, increasingly stronger doses will be administered until an optimum effect is obtained.

20 25 For other patients, it may be necessary to administer maintenance doses 1 to 8 times a day, and preferably 1 to 4 times, according to the physiological requirements of the patient in question. It is also possible that some patients may require the use of only one to two daily administrations.

30 35 40 In man, the doses generally range from 0.01 to 200 mg/kg. For intraperitoneal administration, the doses will generally range from 0.1 to 100 mg/kg, preferably from 0.5 to 50 mg/kg and still more specifically from 1 to 10 mg/kg. For intravenous administration, the doses generally range from 0.1 to 50 mg/kg, preferably from 0.1 to 5 mg/kg and still more specifically from 1 to 2 mg/kg. It is understood that, in order to choose the most suitable dosage, account should be taken of the administration route, the patient's weight, general state of health and age and all factors which may influence the efficacy of the treatment.

45 The example which follows illustrates a composition according to the invention.

#### EXAMPLE

50 40 mg of the product obtained in Example 1 are dissolved in 1 cm<sup>3</sup> of Emulphor EL 620 and 1 cm<sup>3</sup> of ethanol, and the solution is then diluted by adding 18 cm<sup>3</sup> of physiological saline. The composition is administered by perfusion over 1 hour by introduction in physiological solution.

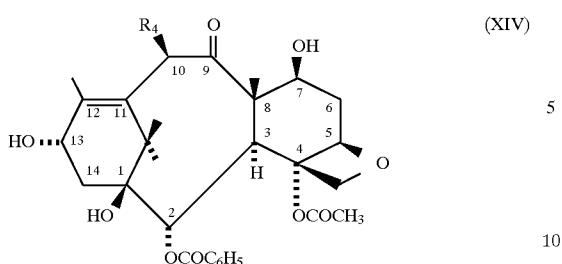
55 We claim:

1. 4 $\alpha$ -Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxo-11-taxen-13 $\alpha$ -yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

2. A pharmaceutical composition comprising at least the product according to claim 1 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

3. A method comprising the step of etherifying selectively at position 7 a compound of the formula (XIV):

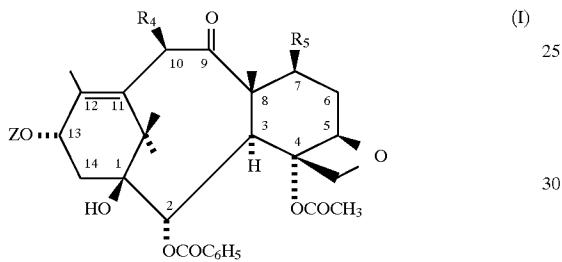
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wherein  $R_4$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,  
with a compound of the formula (XV):



wherein  $R'_5$  represents a radical such that  $R'_5-O$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and  $X_2$  represents a reactive ester residue or a halogen atom, to produce a compound of the formula (I):

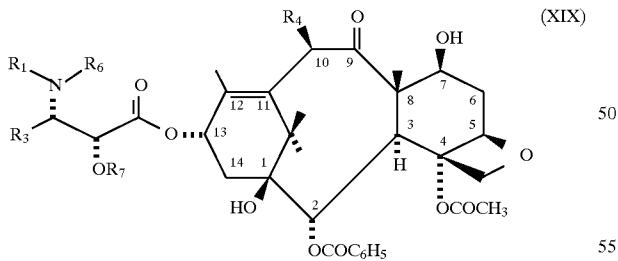


wherein Z is hydrogen,  $R_4$  is as defined above, and  $R_5$  is identical to  $R'_5$  as defined above.

**4.** A method comprising the step of reacting a product of the formula (XV):



wherein  $R'_5$  represents a radical such that  $R'_5-O$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, and  $X_2$  represents a reactive ester residue or a halogen atom, with a compound of the formula (XIX):



wherein  $R_1$  represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a phenoxyl radical,

a furoyl radical, or

a radical  $R_2-O-CO-$  in which  $R_2$  represents:  
an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an

**30**

alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxy carbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or  $\alpha$ - or  $\beta$ -naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

$R_3$  represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or  $\alpha$ - or  $\beta$ -naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxy carbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxy carbonyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy carbonylamino, acyl, aryl carbonyl, cyano, carboxyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl and alkoxy carbonyl radicals,

with the proviso that, in the substituents of the phenyl,  $\alpha$ - or  $\beta$ -naphthyl and aromatic heterocyclic radicals in the definitions of  $R_2$  and  $R_3$ , the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or  $\alpha$ - or  $\beta$ -naphthyl radicals,

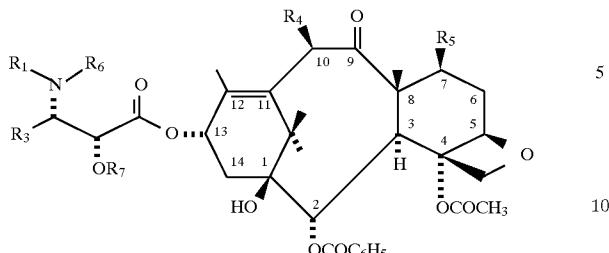
$R_4$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

either  $R_6$  represents a hydrogen atom and  $R_7$  represents a group protecting the hydroxyl function, or  $R_6$  and  $R_7$  together form a saturated 5- or 6-membered heterocycle,

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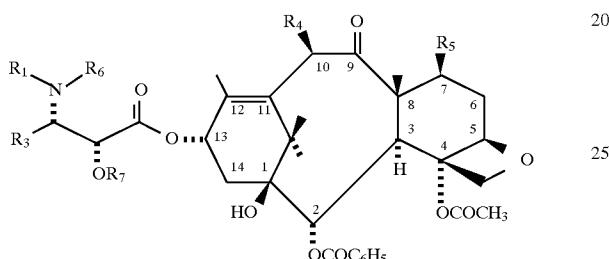
**31**

to form a compound of the formula (V):



wherein R<sub>5</sub> represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and R<sub>1</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, and R<sub>7</sub> are as defined above.

**5.** A method comprising the step of replacing with hydrogen atom(s) group(s) R<sub>6</sub> and R<sub>7</sub> in a compound of the formula (V):



wherein:

R<sub>1</sub> represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R<sub>2</sub>—O—CO— in which R<sub>2</sub> represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkyl radical containing 1 to 4 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxy carbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4

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carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R<sub>3</sub> represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxy carbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxy carbonyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy carbonylamino, acyl, aryl carbonyl, cyano, carboxyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl and alkoxy carbonyl radicals,

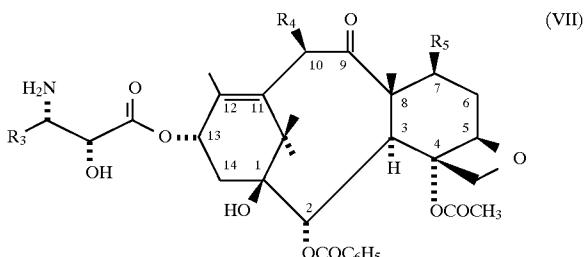
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R<sub>2</sub> and R<sub>3</sub>, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R<sub>4</sub> represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

R<sub>5</sub> represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

either R<sub>6</sub> represents a hydrogen atom and R<sub>7</sub> represents a group protecting the hydroxyl function, or R<sub>6</sub> and R<sub>7</sub> together form a saturated 5- or 6-membered heterocycle,

by treating the compound of formula (V) with an organic or inorganic acid, optionally in an organic solvent to obtain a compound of the formula (VII):



wherein R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are as defined above.

**6.** A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

converting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-

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taxen-13 $\alpha$ -yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate to said 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxo-11-taxon-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

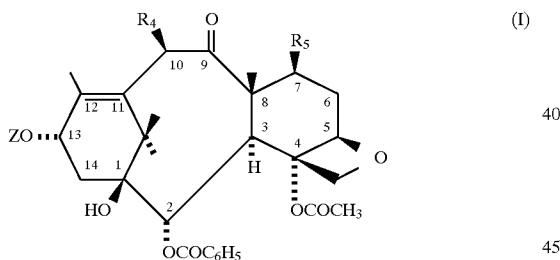
7. A process for the preparation of 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxo-11-taxon-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

(a) reacting 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -7 $\beta$ ,10 $\beta$ -trihydroxy-9-oxo-11-taxon-13 $\alpha$ -yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate with dimethyl sulfoxide in the presence of acetic anhydride and acetic acid to obtain 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -bis(methylthiomethoxy)-9-oxo-11-taxon-13 $\alpha$ -yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate;

(b) reacting the product obtained in (a) with activated Raney nickel to obtain 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxo-11-taxon-13 $\alpha$ -yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate; and

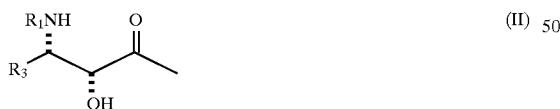
(c) reacting the product obtained in (b) with an acid to obtain 4 $\alpha$ -acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1 $\beta$ -hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxo-11-taxon-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

8. A process for preparing a taxoid of the following formula (I):



in which:

Z represents a radical of formula (II):



in which:

R<sub>1</sub> represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,  
a furoyl radical, or

a radical R<sub>2</sub>—O—CO— in which R<sub>2</sub> represents:  
an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a

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cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxy carbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or  $\alpha$ - or  $\beta$ -naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R<sub>3</sub> represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or  $\alpha$ - or  $\beta$ -naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxy carbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxy carbonyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy carbonylamino, acyl, aryl carbonyl, cyano, carboxyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl and alkoxy carbonyl radicals,

with the proviso that, in the substituents of the phenyl,  $\alpha$ - or  $\beta$ -naphthyl and aromatic heterocyclic radicals in the definitions of R<sub>2</sub> and R<sub>3</sub>, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or  $\alpha$ - or  $\beta$ -naphthyl radicals,

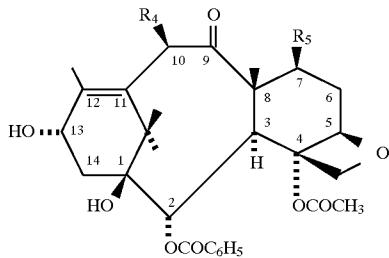
R<sub>4</sub> represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R<sub>5</sub> represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, said process comprising:

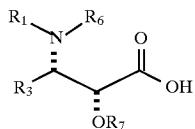
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esterifying a product of formula (III):

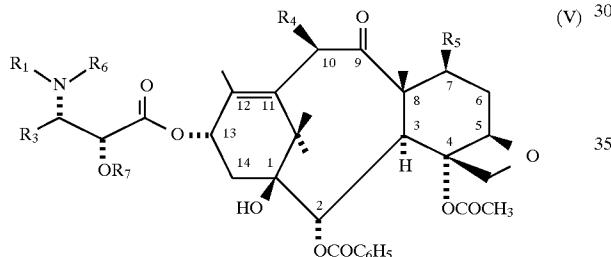


in which  $R_4$  and  $R_5$  are defined as above  
with an acid of formula (IV):



in which  $R_1$  and  $R_3$  are defined as above, and either  $R_6$  represents a hydrogen atom and  $R_7$  represents a group protecting the hydroxyl function, or  $R_6$  and  $R_7$  together form a saturated 5- or 6-membered heterocycle, or

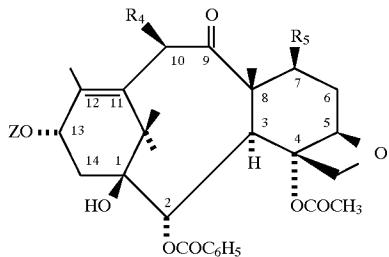
with a derivative of said acid, to obtain an ester of formula (V):



in which  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  and  $R_7$  are defined as above,  
and

replacing the protective group(s) of said ester of formula (V), represented by  $R_7$  or  $R_6$  and  $R_7$  together, by hydrogen atoms.

**9. A process for preparing a new taxoid of the following formula (I):**



in which:

Z represents a hydrogen atom,

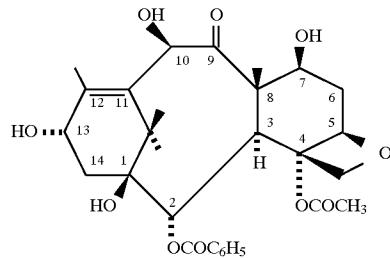
$R_4$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

$R_5$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,  
said process comprising:

(III)

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treating 10-deacetylbaaccatin III of formula (IX):



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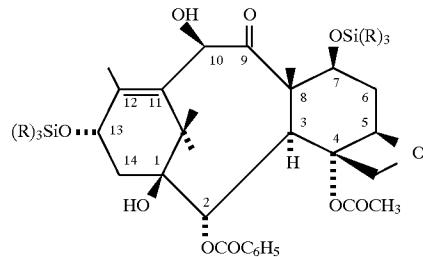
with a silyl halide of formula:

(IV)

 $(R)_3\text{Si}-\text{Hal}$ 

(IX)

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XI):



in which R is defined as above,

treating said product of formula (XI) with a product of formula:

 $R'_4-\text{X}_1$ 

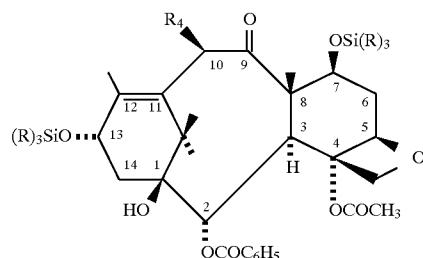
(XII)

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in which  $R'_4$  represents a radical such that  $R'_4-\text{O}$  is identical to  $R_4$  defined above and  $X_1$  represents a halogen atom or a reactive ester residue, to obtain a product of formula (XIII):

(I)

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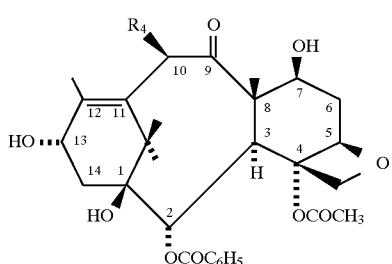


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in which R and  $R_4$  are defined as above,

replacing the silyl protective groups of said product of formula (XIII) by hydrogen atoms to obtain a product of formula (XIV):

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(XIV)

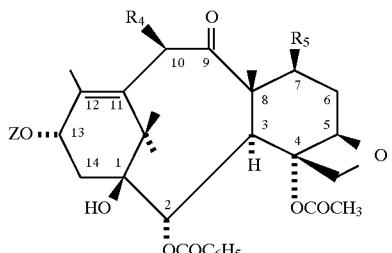
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in which  $R_4$  is defined as above, andetherifying said compound of formula (XIV) selectively  
at position 7 with a product of formula (XV):

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 $R'_5-X_2$ 

(XV)

in which  $R'_5$  represents a radical such that  $R'_5-O$  is identical to  $R_5$  defined as above and  $X_2$  represents a reactive ester residue or a halogen atom, to give the product of formula (I) in which Z represents a hydrogen atom.**10.** A process for preparing a taxoid of the following formula (I):

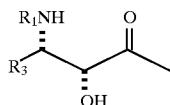
(I) 25

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in which:

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Z represents a radical of formula (II):



(II)

40

in which:

 $R_1$  represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

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a radical  $R_2-O-CO-$  in which  $R_2$  represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which

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each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxy carbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or  $\alpha$ - or  $\beta$ -naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

 $R_3$  represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or  $\alpha$ - or  $\beta$ -naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxy carbonyl amino, amino, alkylamino, dialkylamino, carboxyl, alkoxy carbonyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl, cyano, nitro and trifluoromethyl radicals, or

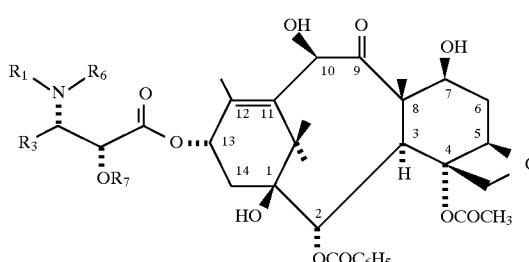
a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy carbonyl amino, acyl, aryl carbonyl, cyano, carboxyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl and alkoxy carbonyl radicals,

with the proviso that, in the substituents of the phenyl,  $\alpha$ - or  $\beta$ -naphthyl and aromatic heterocyclic radicals in the definitions of  $R_2$  and  $R_3$ , the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or  $\alpha$ - or  $\beta$ -naphthyl radicals, $R_4$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and $R_5$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,  
said process comprising:

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treating a product of formula (XVI):

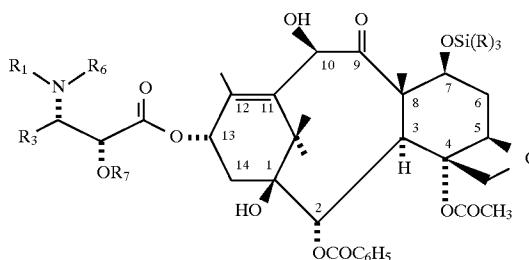


in which  $R_1$ ,  $R_3$ ,  $R_6$  and  $R_7$  are defined as above, with a product of formula (X):

 $(R)_3Si-Hal$ 

(X)

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XVII):



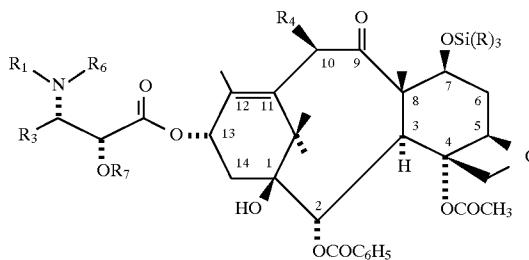
in which R,  $R_1$ ,  $R_3$ ,  $R_6$  and  $R_7$  are defined as above,

functionalizing said compound of formula (XVII) at position 10 with a product of formula:

 $R'_4-X_1$ 

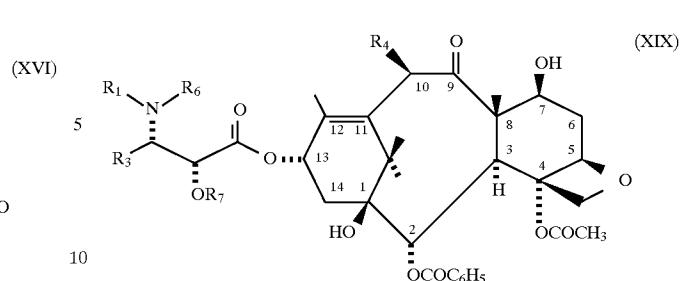
(XII)

in which  $R'_4$  represents a radical such that  $R'_4-O$  is identical to  $R_4$  defined as above and  $X_1$  represents a halogen atom or a reactive ester residue, to give a product of formula (XVIII):



in which R,  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_6$  and  $R_7$  are defined as above,

replacing the silyl protective group of said product of formula (XVIII) by a hydrogen atom to give a product of formula (XIX):

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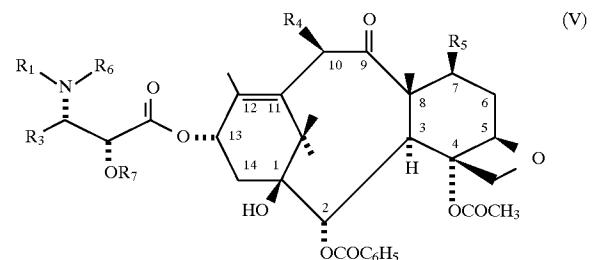
in which  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_6$  and  $R_7$  are defined as above which, when reacted with a product of formula (XV):

 $R'_5-X_2$ 

(XV)

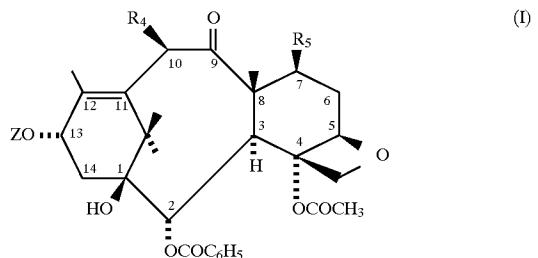
in which  $R'_5$  represents a radical such that  $R'_5-O$  is identical to  $R_5$  defined above and  $X_2$  represents a reactive ester residue or a halogen atom,

yields the product of formula (V):



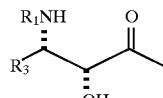
in which  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  and  $R_7$  are defined as above and replacing the protective group(s) of formula (V) with one or two hydrogen atoms to give a product of formula (I) in which Z represents a radical of formula (II).

**11.** A process for preparing a taxoid of the following formula (I):



in which:

Z represents a hydrogen atom or a radical of formula (II):



in which:

$R_1$  represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical  $R_2-O-CO-$  in which  $R_2$  represents:  
an alkyl radical containing 1 to 8 carbon atoms, an  
alkenyl radical containing 2 to 8 carbon atoms, an

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alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarboonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms.

a phenyl or  $\alpha$ - or  $\beta$ -naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or  
 a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

$R_3$  represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or  $\alpha$ - or  $\beta$ -naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxy carbonyl amino, amino, alkylamino, dialkylamino, carboxyl, alkoxy carbonyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy carbonyl amino, acyl, aryl carbonyl, cyano, carboxyl, carbamoyl, alkyl carbamoyl, dialkyl carbamoyl and alkoxy carbonyl radicals,

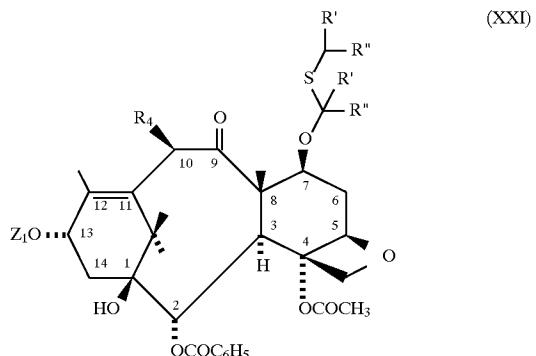
with the proviso that, in the substituents of the phenyl,  $\alpha$ - or  $\beta$ -naphthyl and aromatic heterocyclic radicals in the definitions of  $R_2$  and  $R_3$ , the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or  $\alpha$ - or  $\beta$ -naphthyl radicals,

$R_4$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

$R_5$  represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

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said process comprising reacting activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, with a product of formula (XXI):

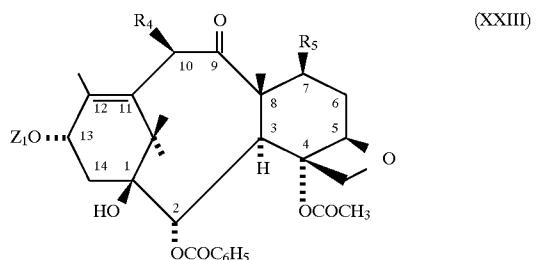


20 in which  $R_4$  is defined as above, and  $R'$  and  $R''$ , which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R'', together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z<sub>1</sub> represents a hydrogen atom or a radical of formula (XXII):



in which  $R_1$  and  $R_3$  are defined as above and either  $R_6$   
 40 represents a hydrogen atom and  $R_7$  represents a group  
 protecting the hydroxyl function, or  $R_6$  and  $R_7$  together form  
 a saturated 5- or 6-membered heterocycle, to obtain a  
 product of formula (XXIII):



55 followed, when  $Z_1$  represents a radical of formula (XXII),  
by replacing the protective group(s) represented by  $R_6$  or  $R_6$   
and  $R_7$  together by hydrogen atoms under the following  
conditions:

1) when  $R_6$  represents a hydrogen atom and  $R_7$  represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

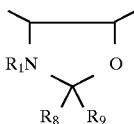
with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrates at a temperature from -10° to 60° C., or

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with a source of fluoride ions, or  
with catalytic hydrogenation, or

2) when R<sub>6</sub> and R<sub>7</sub> together form a saturated 5- or  
6-membered heterocycle of formula (VI):



(VI)

in which R<sub>1</sub> is defined as above and R<sub>8</sub> and R<sub>9</sub>, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R<sub>8</sub> represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R<sub>9</sub> represents a hydrogen atom, or

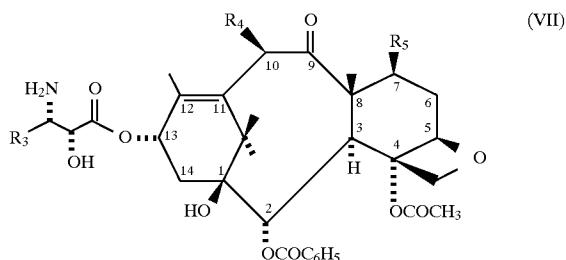
alternatively R<sub>8</sub> and R<sub>9</sub>, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, and further wherein when:

a) R<sub>1</sub> represents a tert-butoxycarbonyl radical and R<sub>8</sub> and R<sub>9</sub>, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R<sub>8</sub> represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R<sub>9</sub> represents a hydrogen atom, or

alternatively R<sub>8</sub> and R<sub>9</sub>, together form a 4- to 7-membered ring, said replacing the protective groups by hydrogen atoms is accomplished

by treating the ester of formula (V) with an inorganic or organic acid, and optionally, with an organic solvent, to obtain the product of formula (VII):



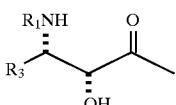
(VII)

in which R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are defined as in claim 1, and acylating said product of formula (VII) with benzoyl chloride in which the phenyl ring is optionally substituted; thenoyl chloride; furoyl chloride; or a product of formula (VIII):



in which R<sub>2</sub> is defined as above and X represents a halogen atom or a residue —O—R<sub>2</sub> or —O—CO—O—R<sub>2</sub>,

to obtain a product of formula (I) in which Z represents a radical of formula (II),



(II)

or

b) R<sub>1</sub> represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R<sub>2</sub>O—CO— in

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which R<sub>2</sub> is defined as above, R<sub>8</sub> represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R<sub>9</sub> represents a hydrogen atom,

said replacing of the protective group formed by R<sub>6</sub> and R<sub>7</sub> together by two hydrogen atoms is accomplished in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons

at a temperature of from -10° to 60° C.

12. A process according to claim 8, wherein said esterifying step is performed with an acid of formula (IV) in the presence of a condensing agent and an activating agent in an organic solvent at a temperature of from -10° to 90° C.

13. A process according to claim 8, wherein said esterifying step is performed with an acid of formula (IV) in the form of the symmetrical anhydride thereof, in the presence of an activating agent in an organic solvent at a temperature of from 0° to 90° C.

14. A process according to claim 8, wherein said esterifying step is performed with the acid of formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base, in an organic solvent at a temperature of from 0° to 80° C.

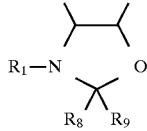
15. A process according to claim 8, further comprising replacing the protective group(s) R<sub>7</sub> or R<sub>6</sub> and R<sub>7</sub> together by hydrogen atoms, wherein:

1) when R<sub>6</sub> represents a hydrogen atom and R<sub>7</sub> represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrates at a temperature from -10° to 60° C., or

with a source of fluoride ions, or  
with catalytic hydrogenation,

2) when R<sub>6</sub> and R<sub>7</sub> together form a saturated 5- or 6-membered heterocycle of formula (VI).



(VI)

in which R<sup>1</sup> is defined as in claim 8 and R<sub>8</sub> and R<sub>9</sub>, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R<sub>8</sub> represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R<sub>9</sub> represents a hydrogen atom, or

alternatively R<sub>8</sub> and R<sub>9</sub>, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, and further wherein when:

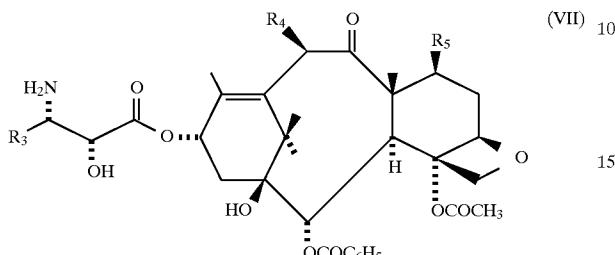
a) R<sub>1</sub> represents a tert-butoxycarbonyl radical and R<sub>8</sub> and R<sub>9</sub>, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

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alternatively R<sub>6</sub> represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R<sub>9</sub> represents a hydrogen atom, or alternatively R<sub>8</sub> and R<sub>9</sub> together form a 4- to 7-membered ring,

the ester of formula (V) is treated with an inorganic or organic acid, and optionally, in an organic solvent, to obtain the product of formula (VII):



in which

R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are defined in claim 8, and said product of formula (VII) is acylated with benzoyl chloride in which the phenyl ring is optionally substituted or thenoyl chloride, or furoyl chloride or a product of formula (VIII):



in which R<sub>2</sub> is defined in claim 8 and X represents a halogen atom or a residue —O—R<sub>2</sub> or —O—CO—O—R<sub>2</sub>, to obtain a product of formula (I) in which Z represents a radical of formula (II),

b) when R<sub>1</sub> represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R<sub>2</sub>O—CO—in which R<sub>2</sub> is defined as above, R<sub>6</sub> represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R<sub>9</sub> represents a hydrogen atom,

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the protective group formed by R<sub>6</sub> and R<sub>7</sub> is replaced by hydrogen atoms in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from -10° to 60° C.

**16.** A process according to claim 15, wherein when R<sub>6</sub> and R<sub>7</sub> together form a saturated 5- or 6-membered heterocycle of formula (VI), and R<sub>8</sub> and R<sub>9</sub> which may be identical or different, represent an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, the aryl portion of said aralkyl radical represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

**17.** A process according to claim 15, wherein when R<sub>6</sub> and R<sub>7</sub> together form a saturated 5- or 6-membered heterocycle of formula (VI), and R<sub>8</sub> and R<sub>9</sub>, which may be identical or different, represent an aryl radical, said aryl radical is a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

**18.** A process according to claim 15, wherein said temperature ranges from 15° to 30° C.

**19.** A process according to claim 15, wherein said source of fluoride ions is a hydrofluoric acid/triethylamine complex.

**20.** A process according to claim 15, wherein said trihalomethyl radical is trichloromethyl.

**21.** A process according to claim 15, wherein when said ester of formula (V) is treated in an organic solvent, said organic solvent is an alcohol.

**22.** A process according to claim 7, wherein said activated Raney nickel is present in step (b) in an ethanolic suspension and further wherein said acid in step (c) is an ethanolic solution of hydrochloric acid.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 5,847,170

Page 1 of 2

DATED : Dec. 8, 1998

INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 4, Column 29, Line 42, after "chain", delete ", ";"

Claim 4, Column 30, Line 63, after "chain", insert --and--;

Claim 4, Column 31, Lines 3-12, to the upper right of the formula, insert --(v)--;

Claim 5, Column 31, Lines 20-29, to the upper right of the formula, insert --(V)--;

Claim 8, Column 33, Line 34, "(1)" should read -(I);

Claim 11, Column 42, Line 66, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 39, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 44, "(VI)." should read --(VI):--;

Claim 15, Column 44, Line 66, after "R<sub>9</sub>", insert --,--;

Claim 15, Column 45, Line 21, after "defined", insert --as--; and

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 5,847,170  
DATED : Dec. 8, 1998  
INVENTOR(S) : Herve Bouchard, et al

Page 2 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 15, Column 45, Line 34, "R6" should read --R<sub>6</sub>--.

Signed and Sealed this

Seventh Day of September, 1999

Attest:



Q. TODD DICKINSON

*Attesting Officer*

*Acting Commissioner of Patents and Trademarks*

# **EXHIBIT B**



US007241907B2

(12) **United States Patent**  
**Didier et al.**

(10) **Patent No.:** US 7,241,907 B2  
(45) **Date of Patent:** Jul. 10, 2007

(54) **ACETONE SOLVATE OF DIMETHOXY DOCETAXEL AND ITS PROCESS OF PREPARATION**

(75) Inventors: **Eric Didier**, Paris (FR); **Marc-Antoine Perrin**, Jouy en Josas (FR)

(73) Assignee: **Aventis Pharma S.A.**, Antony (FR)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 449 days.

(21) Appl. No.: **10/944,254**

(22) Filed: **Sep. 17, 2004**

(65) **Prior Publication Data**

US 2005/0065138 A1 Mar. 24, 2005

**Related U.S. Application Data**

(60) Provisional application No. 60/519,895, filed on Nov. 14, 2003.

(30) **Foreign Application Priority Data**

Sep. 19, 2003 (FR) ..... 03 11016

(51) **Int. Cl.**

**C07D 305/00** (2006.01)

**C07D 407/00** (2006.01)  
**C07D 493/00** (2006.01)

(52) **U.S. Cl. ....** **549/510**

(58) **Field of Classification Search ....** 549/510  
See application file for complete search history.

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

EP	0982027	*	3/2000
WO	WO 96/30355	*	10/1996
WO	WO 97/32869	*	9/1997

\* cited by examiner

*Primary Examiner*—Margaret D. Seaman

*Assistant Examiner*—Niloofer Rahmani

(74) *Attorney, Agent, or Firm*—Balaram Gupta; Paul R. Darkes

(57) **ABSTRACT**

This invention discloses and claims an acetone solvate of dimethoxydocetaxel or 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate and its preparation by crystallization from an aqueous/acetone solution.

**16 Claims, 1 Drawing Sheet**

U.S. Patent

Jul. 10, 2007

US 7,241,907 B2

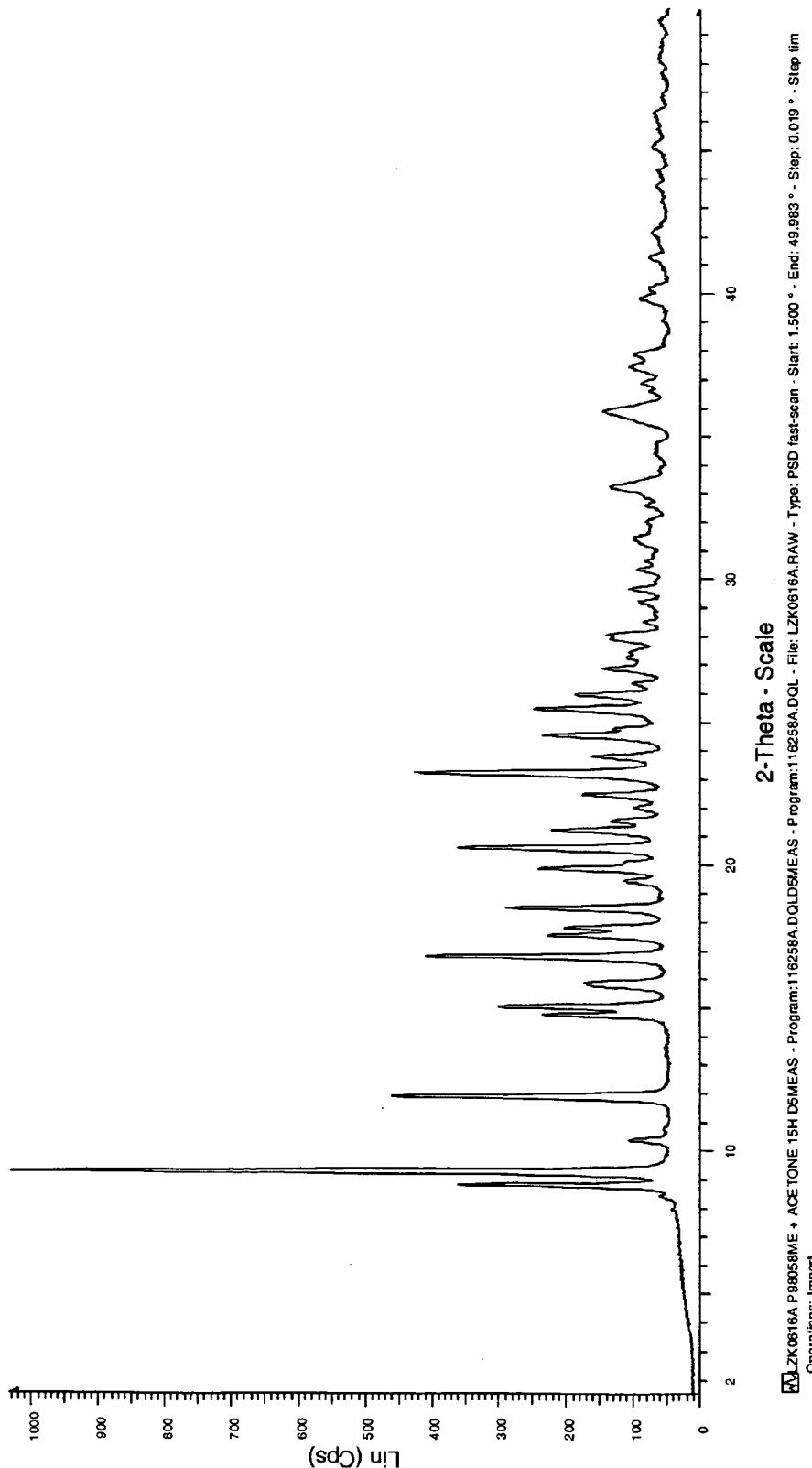


FIG. 1

US 7,241,907 B2

**1**

**ACETONE SOLVATE OF DIMETHOXY  
DOCETAXEL AND ITS PROCESS OF  
PREPARATION**

This application claims the benefit of U.S. Provisional Application No. 60/519,895, filed Nov. 14, 2003 and benefit of priority of French Patent Application No. 03/11,016, filed Sep. 19, 2003, both of which are incorporated herein by reference in their entirety.

**BACKGROUND OF THE INVENTION**

**1. Field of the Invention**

The present invention relates to the acetone solvate of dimethoxydocetaxel or 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate and to its process of preparation.

**2. Description of the Art**

4-Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate exhibits noteworthy anticancer and antileukemic properties.

4-Acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate is prepared according to the process which is disclosed more particularly in international application PCT WO 96/30355 or international application PCT WO 99/25704; according to the process disclosed in these applications, the product is not crystallized and is not characterized.

All of the references described herein are incorporated herein by reference in their entirety.

**SUMMARY OF THE INVENTION**

It has been found that the acetone solvate of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate is fully characterized from a chemical viewpoint.

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 is a powder x-ray diffraction (PXRD) diagram of the acetone solvate form of the product of Example 1.

**DETAILED DESCRIPTION OF THE  
INVENTION**

According to the invention, the acetone solvate of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate can be obtained by crystallization of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate from a mixture of water and of acetone, followed by drying the isolated product under reduced pressure.

For the implementation of the process according to the invention, it can be particularly advantageous to dissolve 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in acetone, to treat the solution with water,

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to seed the solution with a suspension of said product in an acetone/water mixture and then to again treat with water, to separate the crystals obtained, then to dry them under reduced pressure.

Generally, 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate is dissolved in acetone. Preferably, the amount of acetone is between 5 and 20 parts by volume (ml) with respect to the weight (in grams) of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate employed (ideally 10).

The preferred seeding is carried out at a concentration of 60 to 80 g (ideally 68 g) per liter of mixture comprising an acetone/water ratio by volume of from about 65/35 to about 75/25 and preferably of approximately about 68/32. The acetone/water mixture by volume at the end of precipitation is between 70/30 minimum and 30/70 maximum (ideally 45/55). The entire crystallization process takes place, according to a better way of implementing the invention, at 20±5° C. (ideally 20° C.).

The acetone solvate of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate which crystallizes is separated, preferably by filtration or centrifuging. Drying is carried out under a reduced pressure generally of between 0.5 and 30 kPa, preferably in the region of 0.7 kPa, at a temperature of between 30 and 60° C., preferably in the region of 40° C.

The drying of the product was studied. Thus, samples of acetone solvate of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate deliberately treated at a temperature above 70° C. (70 to 100° C.) shows an increasing loss in the content of acetone with the increase in the temperature. For the drying, the preferred temperature is thus between 30 and 60° C. and more preferably still is in the region of 40° C. A mean value of the content of acetone is 7%, which represents approximately the acetone stoichiometry, which is 6.5%, for a solvate comprising one molecule of acetone.

The present invention will be more fully described using the following examples, which should not be regarded as limiting the invention.

**EXAMPLE 1**

940 ml of purified water are added at 20±5° C. ambient temperature to a solution of 207 g of approximately 92% by weight 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl in approximately 2 liters of acetone and then seeding is carried out with a suspension of 2 g of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, isolated from acetone/water, in a mixture of 20 ml of water and 20 ml of acetone. The mixture is left stirring for approximately 10 to 22 hours and 1.5 liters of purified water are added over 4 to 5 hours. The mixture is left stirring for 60 to 90 minutes and then the suspension is filtered under reduced pressure. The cake is washed on the filter with a solution prepared from 450 ml of acetone and 550 ml of purified water and is then dried in an oven at 55° C. under reduced pressure (0.7 kPa) for 4 hours. 197 g of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate are obtained.

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carbonylamino-2-hydroxy-3-phenyl-propionate acetone, comprising 0.1% of water and 7.2% of acetone (theoretically 6.5% for a stoichiometric solvate), are obtained.

## Drying Study

The product is again placed in an oven and successively dried for 18 hours at 60° C. under a reduced pressure of 0.7 kPa, for 3 hours at 60° C. under a relative humidity of approximately 80% (reduced pressure of 160 mmHg) and for 18 hours at 70° C. under a relative humidity of approximately 80% (reduced pressure of 200 mmHg). At this stage, the content of water is 0.2% and the content of acetone is 4.7% (194 g). At this same stage, 1 aliquot of 1 g of the batch is dried under a reduced pressure of 5 mmHg successively for 18 hours at 80° C. (residual acetone content of 0.5%) and then for 21 hours at 100° C. (residual acetone content of 0.02%). The remainder is dried at 80° C. under a reduced pressure of 5 mmHg for 31 hours (acetone 1.7%, water 0.3%, assay with regard to such of 96.5%, purity of greater than 99%).

## Operating Conditions Used for the Acquisition of the PXRD Diagram (FIG. 1)

The analyses are carried out on the Bruker D5000 diffractometer equipped with an Anton Paar TTK temperature chamber. The set-up in reflection possesses focusing geometry of Bragg-Brentano type ( $\theta-\theta$ ). The powder is deposited on a hollow aluminum sample holder. A cobalt anti-cathode tube (40 kV/30 mA) supplies iron-filtered incident radiation. Radiation is emitted at two wavelengths: Co K $\alpha_1$  ( $\lambda=1.7890 \text{ \AA}$ ) and Co K $\alpha_2$  ( $\lambda=1.7929 \text{ \AA}$ ). Filtering by iron does not completely remove the K $\beta$  radiation ( $\lambda=1.6208 \text{ \AA}$  for cobalt), which still participates in the incident radiation at a level of 1% (manufacturer's data) of the intensity of the K $\alpha$  doublet.

Soller slits improve the parallelism of the beam. Variable front slits make it possible to retain a constant illumination area of the sample. A 1 mm collimator limits the scattering between the tube and the measuring chamber. A Braun 50 M multichannel linear detector is used. It exhibits a detection window with a width of 10° of 20 angle. The conditions for recording the diagrams are as follows: scanning from 1.5 to 50° in 20, counting time of 30 seconds per degree in 20, under ambient conditions of temperature, pressure and relative humidity.

FIG. 1 represents the reference PXRD diagram of the solvate form comprising acetone (form A) of the product of example 1.

## NMR Spectrum of the Product of Example 1

$^1\text{H}$  NMR spectrum (400 MHz,  $\text{CDCl}_3$ ,  $\delta$  in ppm): 1.20 (s, 3H), 1.22 (s, 3H), 1.37 (s, 9H), 1.67 (s, 1H), 1.72 (s, 3H), 1.80 (mt, 1H), 1.88 (s, 3H), 2.17 (s, 6H), from 2.20 to 2.40 (mt, 2H), 2.36 (s, 3H), 2.70 (mt, 1H), 3.30 (s, 3H), 3.46 (s, 3H), 3.47 (mt, 1H), 3.82 (d,  $J=7.5 \text{ Hz}$ , 1H), 3.86 (dd,  $J=11$  and  $6.5 \text{ Hz}$ , 1H), 4.17 (d,  $J=8.5 \text{ Hz}$ , 1H), 4.30 (d,  $J=8.5 \text{ Hz}$ , 1H), 4.63 (mt, 1H), 4.80 (s, 1H), 4.97 (broad d,  $J=10 \text{ Hz}$ , 1H), 5.27 (broad d,  $J=10 \text{ Hz}$ , 1H), 5.44 (d,  $J=10 \text{ Hz}$ , 1H), 5.64 (d,  $J=7.5 \text{ Hz}$ , 1H), 6.21 (t,  $J=9 \text{ Hz}$ , 1H), from 7.25 to 7.45 (mt, 5H), 7.49 (t,  $J=7.5 \text{ Hz}$ , 2H), 7.60 (broad t,  $J=7.5 \text{ Hz}$ , 1H), 8.09 (d,  $J=7.5 \text{ Hz}$ , 2H).

What is claimed is:

1. An acetone solvate of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

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2. An acetone solvate of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate comprising from about 5 to about 7 percent by weight of acetone.

3. A process for the preparation of the acetone solvate of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, which comprises:

crystallizing 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate from a mixture of water and acetone, which comprises seeding the solution with a suspension of said product in an acetone/water mixture and then subsequently treating with water, and which comprises drying the product obtained under reduced pressure.

20 4. The process as set forth in claim 3, wherein the seeding is carried out at a concentration of from about 60 to about 80 g per liter of a mixture comprising an acetone/water ratio by volume of from about 65/35 to about 75/25.

25 5. The process as set forth in claim 4, wherein the seeding is carried out in a mixture comprising an acetone/water ratio by volume of about 68/32.

30 6. The process as set forth in claim 3, wherein the acetone/water mixture by volume at the end of precipitation is from about 70/30 to about 30/70.

7. The process as set forth in claim 6, wherein the acetone/water mixture by volume at the end of precipitation is about 45/55.

35 8. The process as set forth in claim 3, wherein the crystallization process takes place at about  $20\pm 5^\circ \text{ C}$ .

9. The process as set forth in claim 4, wherein the crystallization process takes place at about  $20\pm 5^\circ \text{ C}$ .

10. The process as set forth in claim 5, wherein the crystallization process takes place at about  $20\pm 5^\circ \text{ C}$ .

40 11. The process as set forth in claim 6, wherein the crystallization process takes place at about  $20\pm 5^\circ \text{ C}$ .

12. The process as set forth in claim 7, wherein the crystallization process takes place at about  $20\pm 5^\circ \text{ C}$ .

13. The process as set forth in claim 3, wherein drying is carried out at a temperature in the range of from about 30 and about  $60^\circ \text{ C}$ .

45 14. The process as set forth in claim 13, wherein drying is further carried out under a pressure in the region of 0.7 kPa.

15. The process as set forth in claim 3, wherein drying is carried out at a temperature of about  $40^\circ \text{ C}$ . under a pressure in the region of 0.7 kPa.

50 16. The process as set forth in claim 3, wherein the preparation is carried out directly starting from the acetone solution of 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate obtained by deprotection in an acid medium of the ester 4-acetoxy-2 $\alpha$ -benzoyloxy-5 $\beta$ ,20-epoxy-1-hydroxy-7 $\beta$ ,10 $\beta$ -dimethoxy-9-oxotax-11-en-13 $\alpha$ -yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylate.

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